Timo Vesikari
Pierre Van Damme
Editors

Pediatric Vaccines and Vaccinations

A European Textbook

Second Edition

Springer

Pediatric Vaccines and Vaccinations

Timo Vesikari • Pierre Van Damme
Editors

Pediatric Vaccines and Vaccinations

A European Textbook

Second Edition

Springer

Editors
Timo Vesikari
Nordic Research Network Oy
Tampere
Finland

Pierre Van Damme
Centre for the Evaluation
of Vaccination
Vaccine & Infectious
Disease Institute
University of Antwerp
Antwerp
Belgium

ISBN 978-3-030-77172-0 ISBN 978-3-030-77173-7 (eBook)
https://doi.org/10.1007/978-3-030-77173-7

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

A revised edition of the textbook was planned for 2020, 3–4 years after the first edition. The book had been received well by the target audience, both as printed version and, especially, downloads. The feedback by the readers was positive. The book was also used as manual in education programs of medical, biomedical, and pharmacy students as well as in postgraduate medical education, harmonizing information on vaccines and vaccinations within and outside Europe. The plan was to keep the structure and scope of the book the same and update the chapters keeping format the same.

Year 2020 turned out to be the year of a new coronavirus, SARS-CoV-2, the associated disease COVID-19, and an unprecedented rush to vaccine development. In the process, corners have been cut, but by and large, the vaccine development has followed the regular path from phase I to phase III, only at "warp speed," but regulatory reviews and licensures have not been compromised.

New vaccine technologies have been at the forefront of the race. The "winner," the first licensed vaccine against COVID-19, is based on mRNA technology and developed by a German company BioNTech, in partnership with Pfizer. The second type of vaccine that has made a breakthrough in the same race are adenovirus vector-based vaccines, the first of which is often dubbed as "Oxford" vaccine. Other new and conventional (such as inactivated whole virus and protein based) technologies have been applied. COVID-19 vaccines are covered in the book, in a new chapter on coronavirus vaccines and vaccinations.

At the time of writing, it was unclear what the place of pediatric vaccinations will be in the fight against COVID-19. It would seem difficult, or impossible, to eradicate the virus from society without extensive population-based vaccinations which by necessity would include children. Pediatric vaccine trials with COVID-19 vaccines are now being conducted.

In addition to specific vaccines against SARS-CoV-2, a considerable amount of interest has been paid to the "non-specific" effects of vaccinations, a topic that already was well represented in the first edition of this textbook. Now renamed as "repurposed vaccines," both BCG and MMR vaccines appear to have an ameliorating effect on the course of COVID-19 infection and are reviewed in the new edition. The list of such vaccines may still grow.

Other vaccines that have seen a lot of progress between the two editions include RSV vaccines (and immunoglobulins), dengue vaccines, and malaria vaccines, all of which are now covered in the revised chapters. All other chapters are likewise updated and, hopefully, the book will again be an up-to-date resource for the readers.

Timo Vesikari
Tampere, Finland

Pierre Van Damme
Antwerp, Belgium
March 2021

Contents

Contributors

Ron H. Behrens Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK

Shalom Ben-Shimol Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Paolo Bonanni Department of Health Sciences, University of Florence, Florence, Italy

Robb Butler WHO Regional Office for Europe, Copenhagen, Denmark

Ron Dagan Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Pierre Van Damme Centre for the Evaluation of Vaccination, Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp, Belgium

Ener Cagri Dinleyici Eskisehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Eskisehir, Turkey

Kirsty Le Doare Faculty of Medicine and Institute for Life Sciences, University of Southampton and NIHR Southampton Clinical Research Facility and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, Hampshire, UK

Simon B. Drysdale Paediatric Infectious Diseases Research Group & Vaccine Institute, St George's University of London, London, UK

Susanna Esposito Pediatric Clinic, Department of Medicine and Surgery, University of Parma, Parma, Italy

Adam Finn UHB Education Centre, Bristol Children's Vaccine Center, Bristol, UK

Eva P. Galiza Paediatric Infectious Diseases Research Group & Vaccine Institute, St George's University of London, London, UK

Nathalie Garçon Bioaster, Lyon, France

Carlo Giaquinto Department of Women and Child Health, University of Padova, Padova, PD, Italy

Paul T. Heath Paediatric Infectious Diseases Research Group & Vaccine Institute, St George's University of London, London, UK

Ulrich Heininger Pediatric Infectious Diseases and Vaccinology, University of Basel Children's Hospital, Basel, Switzerland

Greet Hendrickx Centre for the Evaluation of Vaccination, Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp, Belgium

Tapani Hovi Finnish Institute for Health and Welfare, Helsinki, Finland

Christine E. Jones Faculty of Medicine and Institute for Life Sciences, University of Southampton and NIHR Southampton Clinical Research Facility and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, Hampshire, UK

Herwig Kollaritsch Institute for Specific Prophylaxis and Tropical Medicine, Medical University of Vienna, Vienna, Austria

Johannes Liese Department of Pediatrics, University of Würzburg, Würzburg, Germany

Kirsten Maertens Centre for the Evaluation of Vaccination, Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp, Belgium

Carlos Martín Departmento de Microbiología y Pediatría, Faculty of Medicine at University of Zaragoza and Steering Committee of Tuberculosis Vaccine Initiative (TBVI), Zaragoza, Spain

CIBER Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain

Servicio de Microbiología, Hospital Universitario Miguel Servet, ISS Aragón, Zaragoza, Spain

Federico Martinón-Torres Translational Pediatrics and Infectious Diseases, Hospital Clínico Universitario de Santiago, A Coruña, Spain

Genetics, Vaccines and Infectious Diseases Research Group (GENVIP), Instituto de Investigación Sanitaria de Santiago, University of Santiago, A Coruña, Spain

Andrew J. Pollard Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford, UK

NIHR Biomedical Research Centre, Oxford University Hospitals NHS Trust, Oxford, UK

Department of Paediatrics, University of Oxford, Level 2, Children's Hospital, Oxford, UK

Natalie Prevatt Whittington Hospital, Whittington NHS Trust, London, UK

Francesca Rocchi University-Hospital Paediatric Department, Bambino Gesù Children Hospital, Rome, Italy

Manish Sadarangani Vaccine Evaluation Center, BC Children's Hospital Research Institute, Vancouver, BC, Canada

Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada

Mary P. E. Slack School of Medicine and Dentistry, Griffith University, Southport, QLD, Australia

Matthew D. Snape Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford, UK

NIHR Biomedical Research Centre, Oxford University Hospitals NHS Trust, Oxford, UK

Vana Spoulou Department of Infectious Diseases, University of Athens, Athens, Greece

Vytautas Usonis Vilnius University Faculty of Medicine, Clinic of Children Diseases, Vilnius, Lithuania

Timo Vesikari Nordic Research Network Oy, Tampere, Finland

Alex Vorsters Centre for the Evaluation of Vaccination, Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp, Belgium

Elizabeth Whittaker Paediatrics, Imperial College London Faculty of Medicine, London, UK

General Vaccinology

Contents

Expected and Unexpected Effects of Vaccination

Federico Martinón-Torres

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_1

1

1.1 Introduction

Vaccination is widely considered to be one of the greatest medical achievements of civilization and one of the top major breakthroughs of humanity.

From an almost empirical origin of vaccinology to the present vaccinomics, our knowledge has evolved substantially and we have learned important lessons. Although the main target of a vaccine is direct protection against a particular microorganism or disease, the scope of vaccination has expanded with the discovery that vaccines can also protect unvaccinated people through herd protection, or even that certain vaccines can protect against additional diseases different from those that they were designed to prevent, through so-called heterologous effects.

1.2 Effectiveness and Impact of Vaccination

Disease prevention through vaccination is the most cost-effective healthcare intervention available. The World Health Organization (WHO) estimates that every year immunization saves between two and three million lives across the world. One hundred years ago, infectious diseases were the main cause of death worldwide, even in the most developed countries. Today, common childhood diseases of previous generations are becoming increasingly rare, thanks to vaccines, and there are new vaccines on the horizon with the potential to prevent even more. Furthermore, existing and newly developed vaccines are targeting other populations or age groups different than children, like pregnant women (pertussis or influenza vaccines) or elderly (pneumococcal or herpes zoster vaccines).

Mass immunization programs have proven successful at controlling or even eliminating disease (Fig. 1.1).

1.2.1 Smallpox

Before a vaccination campaign eliminated all natural occurrences of smallpox in 1977, the disease threatened 60% of the world's population and killed one in four patients.

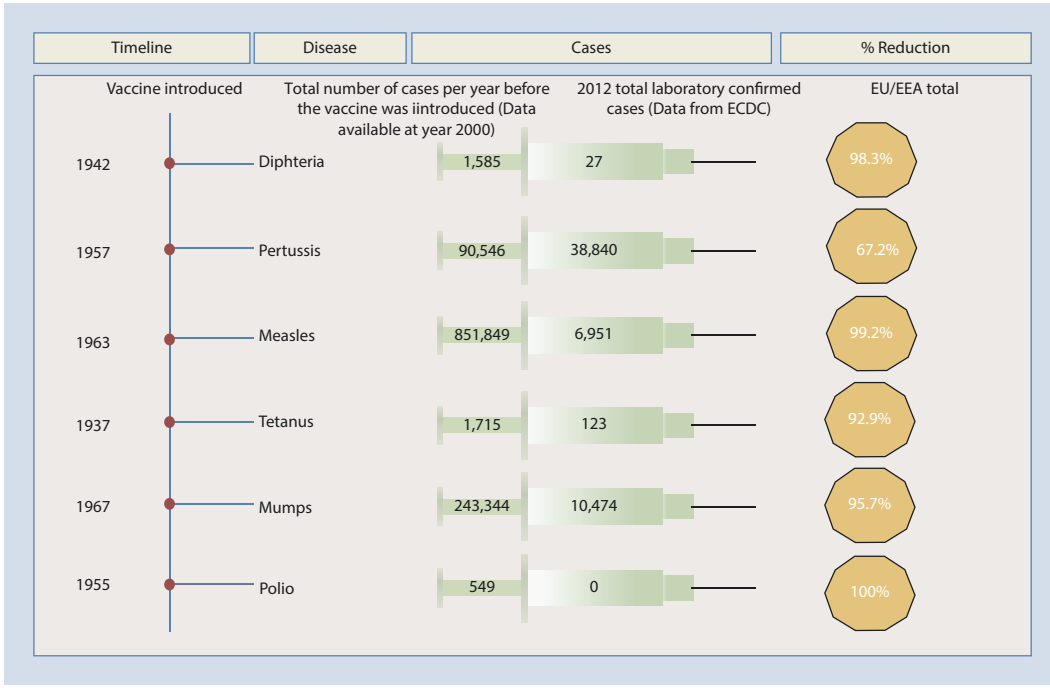


Fig. 1.1 Effectiveness and impact of the introduction of various vaccines in Europe

Approximately 350 million people are estimated to have been spared from smallpox infection and 40 million from dying, since the disease was eradicated.

1.2.2 Measles

Between 2000 and 2014, deaths from measles dropped by 79% worldwide, preventing an estimated 17.1 million deaths and making the measles vaccine one of the best buys in public health. Since 1974, the number of reported measles deaths has dropped from two million to 150,000 per year, although the fight to eradicate the disease is still under way for reasons other than vaccine effectiveness. Measles eradication is in sight if we are able to deal with hesitancy regarding vaccination and anti-vaccine lobbies and to maintain global vaccination coverage at an adequate level (▶ Chap. 9).

1.2.3 Polio

Total eradication of polio is within our reach. Since the creation of the Global Polio Eradication Initiative in 1988 by the WHO and its partners, reported cases of polio have fallen by 99%, with paralysis being prevented in an estimated ten million people (▶ Chap. 8).

1.2.4 Haemophilus

The conjugate vaccines are effective tools for preventing Hib infections, which were the most common severe invasive childhood infections in industrialized countries. Several prospective studies have shown an efficacy exceeding 90% from the first months of life. The impact of vaccination in different European countries is summarized in ◘ Table 1.1 (▶ Chap. 19).

1.2.5 Diphtheria

Before vaccination against diphtheria became readily available in the 1980s, it is estimated that approximately one million cases occurred in the countries of Eastern Europe each year. Although diphtheria is still present in some European countries and epidemics broke out in Eastern Europe during the 1990s, it is now drastically reduced, thanks to vaccination.

1.2.6 Invasive Pneumococcal Disease

Several European countries have reported a significant decline in rates of invasive pneumococcal infection and mucosal forms of pneumococcal disease (mainly otitis and pneumonia) as a result of pneumococcal conjugate vaccination. This benefit also seems to have spread to unvaccinated populations through herd protection.

1.2.7 Invasive Meningococcal Disease

Mass vaccination of children and adolescents with group A + C meningococcal conjugate vaccine, together with routine childhood immunization, has yielded reductions in hospitalization and mortality in Africa. In Europe, meningococcal group C (MenC) infections and deaths decreased by more than 90% after the deployment in 1999 of a vaccination campaign with a MenC conjugate vaccine in the UK. A similar result was found in other countries that included the MenC vaccine in their schedules, such as the Netherlands or Spain. The inclusion of quadrivalent meningococcal conjugate vaccines against serogroups A, C, W, and Y into the national immunization program of different European countries like the UK or the Netherlands had led to a significant reduction of the cases due to serogroup W. Also, the use of infant vaccination programs with the subcapsular antigens-based MenB vaccine (4CMenB) has shown significant impact (UK) and effectiveness (Portugal, Italy) in Europe (▶ Chap. 22).

1.2.8 Rotavirus

Within 8 years of their initial introduction into Europe, rotavirus vaccines have been shown to be highly effective, with a substan-

Table 1.1 Annual *Haemophilus* cases prevented by conjugate vaccines in children aged 0–4 years in various European countries

Country and year of comparison	Number of children 0–4 years old	Incidence before vaccination		Cases/year before vaccination		Incidence after vaccination		Cases prevented by vaccination/year	
		Meningitis	All entities	Meningitis	All entities	Meningitis	All entities	Meningitis	All entities
Scandinavia 1970s vs 1995	1,581,000	31	51	490	810	<1	1	470	770
Austria, Vienna, 1991 vs 1993–1996	485,000	11		55		<1		50	
France – Val-de-Marne, 1980s vs 1992–1993	45,000		21–25	>500	18		4		15
Whole country	3,777,000		23		870		4	420	720
Germany – Rhein–Main area, 1989 vs 1993–1995	100,000		33	950	33	0.8	1	900	1800
Whole country	4,115,000	23	46		1900	0.9	1.3		
Ireland, 1991–1993 vs 1995	260,000		25		65		2.6		60
The Netherlands, 1970s vs 1993–1994	981,000	22–40	80	390	78	0.3	1	385	770
Spain, Basque region, 1993–1995 vs 1997	80,000	14	21	13	18	0	2	13	16
Switzerland, 1976–1990 vs 1991–1993	447,000	26	84	115	375	8	10	80	330
United Kingdom – England and Wales, 1991–1992 vs 1993–1994	3,434,000	15	31	515	1060	0.6	2	500	990
Whole country	3,831,000	24	36	920	1380	0.6	1	895	1340

tial impact on the rotavirus gastroenteritis-related healthcare burden, including hospitalizations, nosocomial infections, and outpatient visits. These findings are consistent in several studies and countries across Europe and comparable with observations from Australia and the USA. Some examples show a >95% effectiveness in the reduction of hospital admissions for rotavirus gastroenteritis in several European countries (Finland, Spain, France, and the UK) and a >60% reduction in the number of hospital admissions and emergency department visits in countries with universal rotavirus vaccination (e.g., Austria, UK, Finland, and Belgium) (▶ Chap. 11).

1.3 Expanded and Unexpected Effects

The main expected benefit from vaccination is protection against the pathogen for which it is designed. This is a direct effect on a particular target infection. For many years, however, epidemiological data indicated some unexpected, beneficial effects were brought about indirectly by some vaccines. These expanded and somewhat unexpected effects have broadened the benefits of vaccines. Using these mechanisms, it is possible to generate direct protection against antigens different from the immunogen contained in the vaccine (cross-protection), protect or even eradicate a disease without having to vaccinate the entire population (indirect or herd protection), or even protect against pathogens different from those targeted by the vaccine (heterologous protection).

1.3.1 Cross-Protection and Heterologous Immunity

The concept of cross-protection denotes the ability of the immune system to recognize various antigens that differ from the immunogen, through certain flexibility in peptide recognition (*cross-immunity*) (◘ Fig. 1.2). For this reason, different antigens appear similar to the immune system, thereby challenging the theoretical specificity postulated by the clonal selection theory. To understand this issue, it is useful to distinguish between cross-neutralization and cross-protection. In *cross-neutralization*, antibodies elicited by vaccination with a certain serotype neutralize other serotypes in vitro. *Cross-protection* means that immunization with a certain vaccine type provides clinically significant protection against infection or disease (or both) owing to another serotype, i.e., that the cross-neutralizing response has a functional impact.

One example is the HPV vaccine. Immunity to HPV is type-specific. However, if we look at the phylogenetic tree that includes the various HPV types, we observe that some degree of cross-protection is possible, given the high level of homology of some viral types with vaccine types. This is the case, for instance, for HPV-31 and HPV-35 (strictly related to HPV-16) and for HPV-45 (strictly related to HPV-18). Another example can be seen with rotavirus vaccines. The antibodies elicited by these vaccines not only protect against those circulating strains sharing the same G or P variant as that contained in the vaccine strain but also other non-matching G and P strains (heterotypic protection). According to this, type-specific antibodies targeted at neutralizing VP7 or VP4 epitopes are not solely responsible for their protective effect. The comparable effectiveness of RV1 and RV5 reinforces this conclusion: neutralizing antibody titers induced by RV1 or RV5 consistently underestimates the protection conferred by the vaccine. Other examples of this cross-reactivity have been confirmed in humans, involving influenza virus-specific immunity or pneumococcal conjugate vaccines, among others.

Cross-protection was described five decades ago and later termed *heterologous immunity*. The initial observation was that $CD8^+$ T cells are able to cross-recognize peptides from two distinct viruses and may play roles not only in protective immunity but also in immunopathology (autoimmunity). According to this phenomenon, memory T cells that are specific to one pathogen can become activated during infection with an unrelated heterologous pathogen. As such,

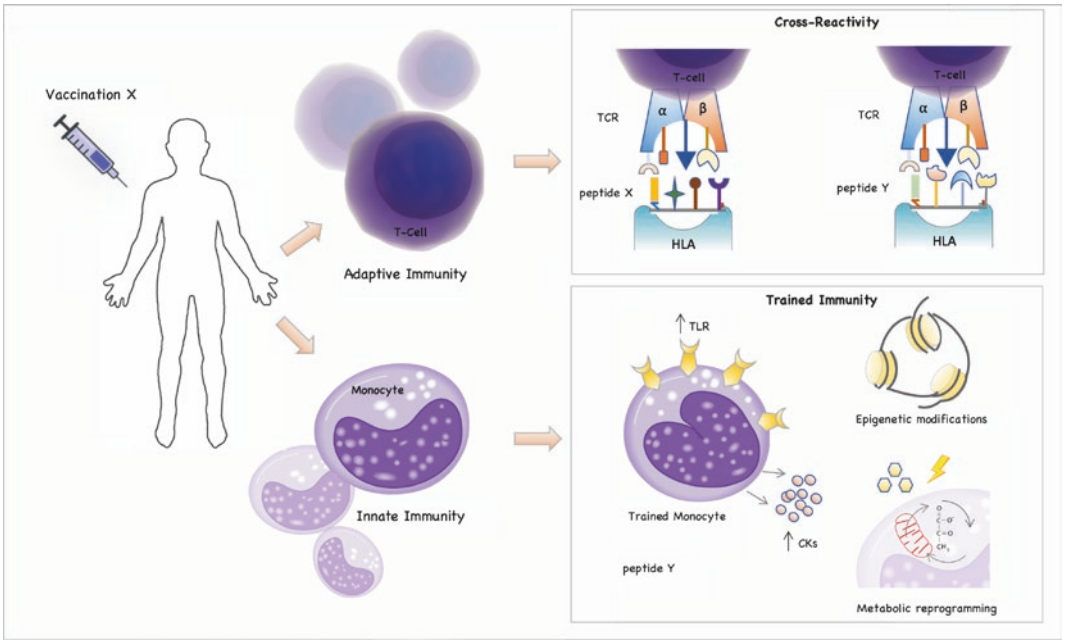


Fig. 1.2 Heterologous immunity. The concept of heterologous immunity includes both components of the immune system: Adaptive T cells can recognize cross-reactive peptides by alternative recognition of TCR, and "trained" monocytes of innate system respond more efficiently to a non-related peptide in a process termed "trained immunity." See text for more detailed explanation

previous host exposure to unrelated infectious agents can greatly alter immune response to an infection. T cells recognize processed peptides that are presented at the cell surface in antigen-binding grooves of class I major histocompatibility class (MHC) proteins. At the same time, the T-cell receptor (TCR) binds to the peptide-MHC complex. Thus, a TCR that recognizes a given MHC-presented peptide may also recognize other peptides that fit into the appropriate MHC groove and have amino acid chains that are able to bind to TCR. This degeneration of the T-cell recognition is called *molecular mimicry* when the cross-reactive peptide has similar determinants and interacts with TCR in the same manner as the original peptide. It is called *alternative recognition* when different determinants of the TCR are involved in recognition. A third explanation for cross-reactivity is when a given T cell expresses two different TCRs as a result of an incomplete allelic exclusion of a second TCR chain; in this way, the two distinct TCRs formed may recognize different antigens.

When the term cross-protection is applied to *vaccination*, it typically refers to *heterosubtypic immunity* defined as protection by virus (influenza is the best-known case) of one strain against a challenge infection with other strains differing in subtype. However, very recently, cross-protective immunity has also been highlighted as one of the mechanisms for the unexpected beneficial effects of BCG vaccination on infections other than tuberculosis. Researchers showed that BCG vaccination induces a long-lasting, nonspecific potentiation effect of heterologous T-helper responses, Th1 (IFN-gamma) and Th17 (IL-17 and IL-22), to non-mycobacterial stimulation. Previously, other authors had demonstrated that both effector and memory CD8+ cells had the potential to secrete IFN-gamma in the absence of related antigens. According to these findings, vaccination can provide not only a heterosubtypic protection but also heterologous protection through a cross-immunity mechanism.

1.3.2 Indirect Protection

The term "herd protection or herd immunity" was coined a century ago, but its use has become widespread in recent decades to describe the reduced risk of infection among susceptible individuals in a population, induced by the presence and proximity of vaccinated individuals. Herd immunity makes it possible to protect a whole community from infectious disease by immunizing a critical percentage of the population. Just as a herd of sheep uses its sheer number to protect individual members from predators, herd immunity protects a community from infectious disease by virtue of the number of immune individuals. The more members of a human herd are immunized, the better protected the whole population will be from an outbreak of disease.

The terms *herd immunity* and *herd effect* are frequently used indistinctly, but they do not reflect the same concept. *Herd immunity* refers only to the proportion of subjects immunized in a given population, while the *herd effect (or herd protection)* is used to describe the indirect protection observed in the non-immunized segment of the population. Furthermore, herd immunity applies to immunization or infection, human to human transmission. Conversely, the herd effect applies exclusively to immunization achieved by vaccination or other health interventions that reduce the probability of transmission.

Vaccination has been revealed as an indirect way of protecting members of the community who cannot be vaccinated. Vaccinated individuals protect themselves from disease, but also, moreover, they prevent the spread of the infectious agent and limit potential disease outbreaks. The herd effect achieved through vaccination for a given disease depends on the efficacy and coverage of the vaccine in addition to the transmissibility of the infection.

There are numerous examples of herd immunity, illustrating the importance of indirect protection for predicting the impact of vaccination programs. The basis for the herd effect is that individuals who are immune to a disease act as a barrier in the spread of disease, slowing or preventing the transmission of disease to others. When a given proportion of the population – known as the herd immunity threshold – becomes immunized, the disease may no longer persist in this population. This threshold is defined based on the "basic reproduction number" (R_0), which represents the number of people in an unprotected population that could receive the disease from one infected individual. The more contagious the disease, the higher this number, and thus the higher the threshold to be reached to protect the community. For example, measles, an extremely contagious disease, has a threshold of 95% to ensure community protection. On the other hand, mumps, which is not as contagious, needs a threshold of 80% (◘ Fig. 1.3, ◘ Table 1.2).

Vaccines can either only protect against the development of clinical disease or prevent the infection also, which impacts vaccination strategy and policy. It is often difficult to establish this difference for a particular vaccine, but it heavily influences the establishment of herd immunity by reducing transmission in the community. A clear example of herd protection is the case of the meningococcal serogroup C conjugate vaccine in the UK, the Netherlands, and subsequently in other countries. The impact of this vaccine on the prevalence of the disease was higher than expected according to the population covered with the vaccine, also reducing the number of cases in a nonvaccinated population. This indirect protection was due to the high efficacy of the vaccination at preventing nasopharyngeal carriage and, thus, spreading of the pathogen to the rest of the population.

Mass vaccination is the best way to rapidly increase herd immunity either for accelerating disease control and to rapidly increase coverage with a new vaccine or in the setting of an existing or potential outbreak, thereby limiting the morbidity and mortality that might result.

Even if the increase in population immunity is not sufficient to achieve infection elimination owing to low vaccine efficacy or insufficient coverage, the risk of infection among unvacci-

1

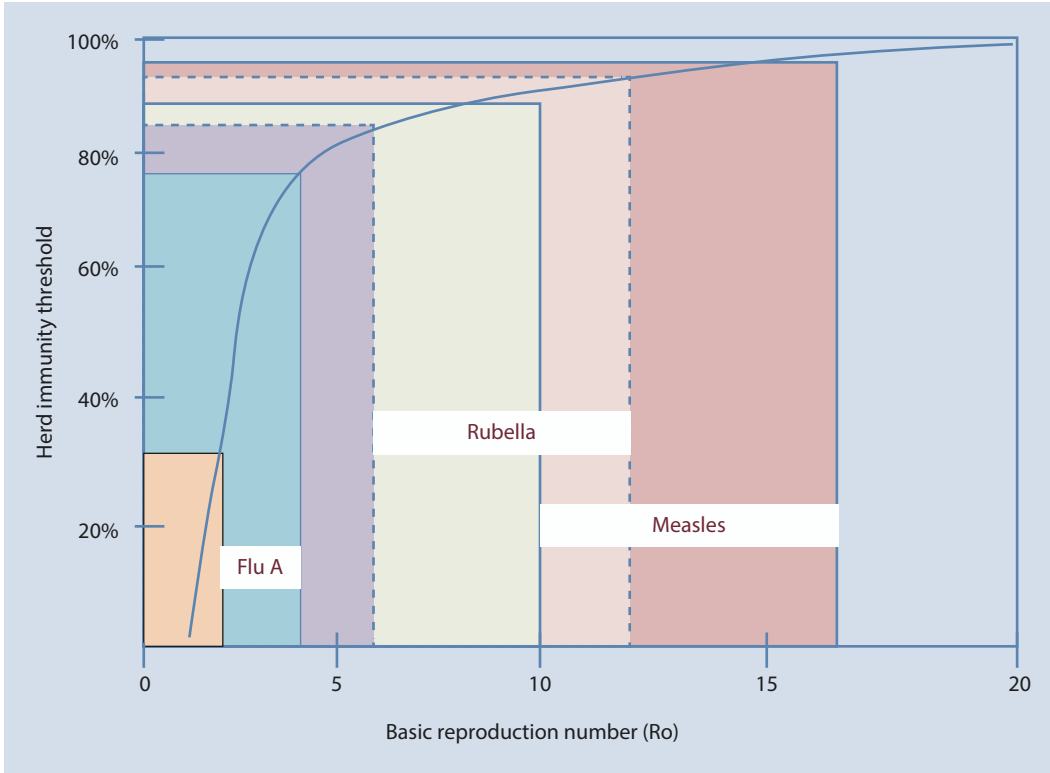


Fig. 1.3 Simple threshold concept of herd immunity. Relationship between the herd immunity threshold, $(R_0 - 1)/R_0 = 1 - 1/R_0$, and basic reproduction number, R_0, in a randomly mixing homogeneous population. Note the implications of ranges of R_0, which can vary considerably between populations, for ranges of immunity coverage required to exceed the threshold

Table 1.2 R_0 values for well-known infectious diseases and herd immunity threshold

Infection	Basic reproduction number (R_0)	Herd immunity threshold (%)	Vaccine efficacy (%)	Vaccine effectiveness (%)
Measles	12–18	55–94	94	90–95
Pertussis	12–17	92–94	70–90	75–85
Polio	12–15	50–93	80–90	90
Varicella	8–10	87–90	90–98	95
Diphtheria	6–7	85	97	95
Rubella	6–7	83–85	94–95	95
Smallpox	5–7	80–85	90–97	?
Mumps	4–7	75–86	95	78
SARS-CoV-2	2.5–5.8	60–83	60–95	?
Spanish flu 1918	2–3	50–67	?	?
Ebola	1.5–2.5	33–60	95–100	70
Cholera	1–2	50	42–66	86

nated persons may still be reduced. This may be particularly important for those for whom vaccination is contraindicated. The paradox is that for an individual, with regard to vaccination in a population, the best option is that everybody else is vaccinated and the individual is not. This way the individual is protected from infection because of the herd effect, but suffers none of the potential adverse effects of vaccination. Finally, these indirect effects may eventually be deleterious, if as a consequence of reducing the risk of infection among those susceptible, there is a displacement of the risk of infection to other age groups and/or to a more vulnerable population, as has been suggested for varicella or hepatitis A in certain scenarios.

1.3.3 Heterologous (Nonspecific) Effects of Vaccination

Some vaccines can broadly enhance immune responses to a range of distinct pathogens or even to other vaccines, indicating that immune protection may be influenced by previous exposure to unrelated microorganisms or microbial components. First described for BCG vaccine, epidemiologists showed a reduction in all-cause mortality or hospitalization rates in the BCG-vaccinated population versus the nonvaccinated that could not be explained by the reduction in deaths due to the prevented pathogen. In recent years, a plethora of scientific papers have documented this unexpected effect of vaccination and explained it as resulting from an indirect action of vaccines on the immune system, other than their specific expected effect. These so-called heterologous or nonspecific effects of vaccines are now being explored not only for BCG – the most frequently studied in this regard – but also for polio, measles, influenza, rotavirus, and others. Scientific data reveal a dual mechanism for these heterologous properties of vaccines: cross-protective immunity (an old and well-known phenomenon described above) and training of innate immune cells, a new and revolutionary concept referring to the innate immunological memory and its ability to be trained through vaccination-induced epigenetic changes.

Immunological memory, or the ability to remember the encounter with a pathogen, used to be considered an exclusive virtue of the adaptive immune system. For some years now, this concept is changing, and immunological memory is recognized too as an ability of the innate host defense. *Immune training* is the term applied to this recently described feature of innate immunity, and its demonstration in humans was first documented with BCG vaccination by Kleinnijenhuis et al.: they showed a BCG-induced trained immunity mechanism of nonspecific protection from infections through epigenetic reprogramming of innate immune cells as monocytes. This revolutionary concept represents a plausible explanation for the rapid protective effects observed after BCG vaccination, unexplained by the cross-protective effect of the adaptive system – the latter, with long-term effects but slow to develop (Fig. 1.2).

According to this concept, vaccination would induce an enhanced innate immunity state mediated by natural killer or monocytes/macrophages, which would provide nonspecific protection against non-related infections. As a consequence of vaccination, innate immune cells become more efficient cells and better responders against microbial aggressions. Epigenetic and metabolic modifications during innate cell development in the bone marrow would be responsible for the maintenance of these enhanced features to influence the functions of innate cells for longer periods. Epigenetic reprogramming of cells through tri-methylation of histones leads to a stronger gene transcription upon re-stimulation through the NOD2 receptor, an intracellular pattern recognition receptor (PRR). Metabolic processes would also be affected, with a cell metabolic shift toward an aerobic glycolytic (transformation of pyruvate to lactate) pathway, as opposed to the classic and less efficient aerobic oxidative phosphorylation of pyruvate. This shift of glucose metabolism is also known as the "Warburg effect" and allows the rapid production of energy for the proliferation of cancer cells or activated lymphocytes.

This epigenetic and metabolic reprogramming is not the only mechanism involved in the immune training of innate cells. Other mechanisms include an increased expression of PRRs on the cell surface following vaccination and enhanced cytokine release, particularly inflammatory signals for a protective function.

Future research should seek a better understanding of innate immune training mechanisms induced by vaccines, including the impact of age, gender, host genetics, geographical location, and sociological factors. It is also important to explore the timing and the combination of vaccines to avoid negative side effects and fully exploit their potential benefits. This will help us to improve the beneficial heterologous effects of vaccination. In addition, vaccines that were removed from the immunization schedule could now be reconsidered in view of these beneficial nonspecific effects.

Positive Heterologous (Nonspecific) Effects

The paradigmatic case of vaccines providing heterologous benefits is that of *bacillus Calmette–Guérin* (BCG). Several randomized controlled trials have indicated that BCG, a vaccine introduced in 1921 to fight against tuberculosis, has beneficial, heterologous, nonspecific effects in children from developing countries, reducing morbidity and mortality caused by unrelated pathogens. Old epidemiological data had already pointed toward a protective nonspecific effect, without a mechanism that could explain it. More recently, it has been demonstrated that this beneficial effect was not restricted to developing countries, with reduced early childhood hospitalization rates owing to respiratory infections and sepsis also observed in high-income settings. Interestingly, these beneficial effects on all-cause mortality are greater for girls than for boys.

Apart from this heterologous effect on all-cause mortality and hospitalization of children, BCG has been revealed in recent years to be a potent immunomodulator, with potential applications in the treatment of immune-based disorders (type 1 diabetes and multiple sclerosis) and as immunotherapy for treating early-stage bladder cancer. Based on this "trained immunity" effect, BCG vaccination is being explored as a potential tool in the management of SARS-COV-2 pandemic. Several ongoing trials are aiming to assess whether BCG vaccination might prevent the clinical infection or ameliorate the course of COVID-19 disease (▶ Chap. 17).

There are, however, reports describing heterologous effects for other vaccines, either live or attenuated. Similar to the BCG vaccine, *measles-containing vaccines* have been demonstrated to reduce mortality and hospital admissions from causes other than measles infection, in both low- and high-income countries. Incidence of infectious diseases other than measles has been found to correlate strongly with incidence of measles in different countries, in both pre- and post-vaccine periods. It has been recently described that the prevention through vaccination of immunosuppressive effects of measles infection – that actually depletes the existing immune memory of the infected host – might explain these long-term benefits of measles vaccination. According to this, measles vaccine expanded benefit actually relates directly to the avoidance of the immunological consequences of the natural infection and the reduction of non-related diseases during the "immune amnesia" period.

The effect of *oral polio vaccine* (OPV) on mortality has only been assessed in a few studies, which concluded that OPV is associated with lower infant mortality and morbidity through these nonspecific effects. The observations of this beneficial effect of OPV have generated a controversial debate on the substitution of oral polio vaccine for the inactivated polio vaccine, and the possible consequences of this decision on the mortality increment, particularly in high-mortality settings.

Rotavirus vaccination has been linked to a decrease in seizure hospitalizations in children. It is not clear if this proposed effect of rotavirus vaccines could be an unexpected direct effect through prevention of systemic rotavirus infection, or it could be a true indirect effect through a mechanism not yet estab-

lished. Similarly, rotavirus vaccination has been epidemiologically linked to a decrease of the incidence of autoimmune diseases as type 1 diabetes and celiac disease.

Rabies vaccine (a nonlive vaccine) has shown protective nonspecific effects in people and in animals. The mechanism is unknown, and a nucleoprotein present in the vaccine has been pointed as a potential immune enhancer. Rabies vaccine was used as the control vaccine in a randomized trial of a malaria vaccine candidate in children, and a significant decrease of all-cause meningitis and cerebral malaria was found in the rabies vaccine arm. Rabies vaccine heterologous effects are now being studied in randomized controlled trials.

Negative Heterologous Effects

Negative heterologous effects might be also possible. An association between the AS03-adjuvanted influenza pandemic vaccine and the development of narcolepsy has been described in some children and infants due to cross-reactivity to host antigens. In this case, molecular mimicry between a fragment of one of the influenza antigens (nucleoprotein) and a portion of the human brain receptor that promotes wakefulness (hypocretin receptor 2) has been suggested as an explanation for this heterologous effect.

Unlike BCG, measles vaccine or OPV, the diphtheria–tetanus–pertussis (DTP) vaccine has not shown the same beneficial effect, and in fact some studies have suggested detrimental effects on children's survival. In 2013, a strategic advisory group of experts commissioned by the WHO reviewed all evidence concerning possible nonspecific effects of DTP-containing vaccines on survival and all-cause mortality in children under 5 years of age, concluding that findings on DTP vaccines were inconsistent. Further research into the potential nonspecific effects of DTP vaccines is warranted. Based on current knowledge, it is suggested that the order in the administration of DTP vaccines with other scheduled vaccines (especially BCG) is important in the generation of these nonspecific effects, as DTP seems to oppose the positive heterologous effects of live vaccines.

In summary, vaccine effectiveness and impact have exceeded expectations, often ahead of our actual understanding of all the mechanisms behind this success. We are now beginning to understand these mechanisms for the oldest vaccines and are now applying this knowledge to the design of the next generation of vaccines.

Further Reading

Aaby P, Roth A, Ravn H, et al. Randomized trial of BCG vaccination at birth to low-birth-weight children: beneficial non-specific effects in the neonatal period? J Infect Dis. 2011;204:245–52.

Benn CS, Jacobsen LH, Fisker AB, Rodrigues A, Sartono E, Lund N, Whittle HC, Aaby P. Campaigns with oral polio vaccine may lower mortality and create unexpected results. Vaccine. 2017;35(8):1113–6. https://doi.org/10.1016/j.vaccine.2016.11.006.

Byberg S, Thysen SM, Rodrigues A, Martins C, Cabral C, Careme M, Aaby P, Benn CS, Fisker AB. A general measles vaccination campaign in urban Guinea-Bissau: comparing child mortality among participants and non-participants. Vaccine. 2017;35(1):33–9. https://doi.org/10.1016/j.vaccine.2016.11.049.

Contreras G. Effect of the administration of oral poliovirus vaccine on infantile diarrhoea mortality. Vaccine. 1989;7:211–2.

De Castro MJ, Pardo-Seco J, Martinon-Torres F. Nonspecific (heterologous) protection of neonatal BCG vaccination against hospitalization due to respiratory infection and sepsis. Clin Infect Dis. 2015;60:1611–9.

Divangahi M, Aaby P, Khader SA, Barreiro LB, Bekkering S, Chavakis T, van Crevel R, Curtis N, DiNardo AR, Dominguez-Andres J, Duivenwoorden R, Fanucchi S, Fayad Z, Fuchs E, Hamon M, Jeffrey KL, Khan N, Joosten LAB, Kaufmann E, Latz E, Matarese G, van der Meer JWM, Mhlanga M, Moorlag SJCFM, Mulder WJM, Naik S, Novakovic B, O'Neill L, Ochando J, Ozato K, Riksen NP, Sauerwein R, Sherwood ER, Schlitzer A, Schultze JL, Sieweke MH, Benn CS, Stunnenberg H, Sun J, van de Veerdonk FL, Weis S, Williams DL, Xavier R, Netea MG. Trained immunity, tolerance, priming and differentiation: distinct immunological processes. Nat Immunol. 2021 Jan;22(1):2−6. https://doi.org/10.1038/s41590-020-00845-6.

Do VA, Biering-Sørensen S, Fisker AB, Balé C, Rasmussen SM, Christensen LD, Jensen KJ, Martins C, Aaby P, Benn CS. Effect of an early dose of measles vaccine on morbidity between 18 weeks and 9 months of age: a randomized, controlled trial in Guinea-Bissau. J Infect Dis. 2017. pii:jiw512. https://doi.org/10.1093/infdis/jiw512.

Domínguez-Andrés J, van Crevel R, Divangahi M, Netea MG. Designing the Next Generation of Vaccines: Relevance for Future Pandemics. mBio. 2020 Dec 22;11(6):e02616–20. https://doi.org/10.1128/mBio.02616-20. PMID: 33443120.

Fine PE. Herd immunity: history, theory, practice. Epidemiol Rev. 1993;15:265–302.

Gómez-Rial J, Rivero-Calle I, Salas A and Martinón-Torres F. Rotavirus and autoimmunity. J Infect (2020) 81(2):183-189

Goodridge HS, Ahmed SS, Curtis N, Kollmann TR, Levy O, Netea MG, Pollard AJ, van Crevel R, Wilson CB. Harnessing the beneficial heterologous effects of vaccination. Nat Rev Immunol. 2016;16(6):392–400. https://doi.org/10.1038/nri.2016.43.

Jensen KJ, Karkov HS, Lund N, et al. The immunological effects of oral polio vaccine provided with BCG vaccine at birth: a randomised trial. Vaccine. 2014;32:5949–56.

Jensen KJ, Benn CS, van Crevel R. Unravelling the nature of non-specific effects of vaccines-A challenge for innate immunologists. Semin Immunol. 2016;28(4):377–83. https://doi.org/10.1016/j.smim.2016.05.005.

John TJ, Samuel R. Herd immunity and herd effect: new insights and definitions. Eur J Epidemiol. 2000;16:601–6.

Kandasamy R, Voysey M, McQuaid F, de Nie K, Ryan R, Orr O, Uhlig U, Sande C, O'Connor D, Pollard AJ. Non-specific immunological effects of selected routine childhood immunisations: systematic review. BMJ. 2016;355:i5225. https://doi.org/10.1136/bmj.i5225.

Kennedy RB, Ovsyannikova IG, Palese P, Poland GA. Current Challenges in Vaccinology. Front Immunol. 2020 Jun 25;11:1181. https://doi.org/10.3389/fimmu.2020.01181.

Kleinnijenhuis J, Quintin J, Preijers F, et al. Bacille Calmette-Guerin induces NOD2-dependent non-specific protection from reinfection via epigenetic reprogramming of monocytes. Proc Natl Acad Sci U S A. 2012;109:17537–42.

Kühtreiber WM, Tran L, Kim T, Dybala M, Nguyen B, Plager S, Huang D, Janes S, Defusco A, Baum D, Zheng H, Faustman DL. Long-term reduction in hyperglycemia in advanced type 1 diabetes: the value of induced aerobic glycolysis with BCG vaccinations. NPJ Vaccines. 2018 Jun 21;3:23. https://doi.org/10.1038/s41541-018-0062-8.

Lund N, Andersen A, Hansen AS, et al. The effect of oral polio vaccine at birth on infant mortality: a randomized trial. Clin Infect Dis. 2015;61:1504–11.

Mina MJ, Metcalf CJ, de Swart RL, Osterhaus AD, Grenfell BT. Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality. Science. 2015;348:694–9.

Mantovani A, Netea MG. Trained Innate Immunity, Epigenetics, and Covid-19. N Engl J Med. 2020 Sep 10;383(11):1078-1080. https://doi.org/10.1056/NEJMcibr2011679

Netea MG. Training innate immunity: the changing concept of immunological memory in innate host defence. Eur J Clin Investig. 2013;43:881–4.

Netea MG, Domínguez-Andrés J, Barreiro LB et al. Defining trained immunity and its role in health and disease. Nat Rev Immunol (2020) 20(6): 375-388

Pollard AJ, Bijker EM. A guide to vaccinology: from basic principles to new developments. Nat Rev Immunol. 2020 Dec 22:1–18. https://doi.org/10.1038/s41577-020-00479-7.

Pollard AJ, Finn A, Curtis N. Non-specific effects of vaccines: plausible and potentially important, but implications uncertain. Arch Dis Child. 2017 pii: archdischild-2015-310282. https://doi.org/10.1136/archdischild-2015-310282. [Epub ahead of print] Review.

Rivero-Calle I, Gomez-Rial J, Martinon-Torres F. Systemic features of rotavirus infection. J Infect. 2016;72(Suppl):S98–S105.

Shann F. The heterologous (non-specific) effects of vaccines: implications for policy in high-mortality countries. Trans R Soc Trop Med Hyg. 2015;109:5–8.

Trotter CL, Maiden MC. Meningococcal vaccines and herd immunity: lessons learned from serogroup C conjugate vaccination programs. Expert Rev Vaccines. 2009;8:851–61.

How Vaccinating People Can Also Protect Others

Adam Finn

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_2

2

2.1 Smallpox Was Not Eradicated by Immunising Everyone

Edward Jenner demonstrated direct protection against smallpox in a human challenge study in a single subject conducted a century before the pioneering work of Pasteur and Koch laid the foundations of our current understanding of the microbial causes of infection. His paper "On the origin of the vaccine inoculation" published in 1801 concludes with the words: "…and it now becomes too manifest to admit of controversy, that the annihilation of the Small Pox, the most dreadful scourge of the human species, must be the final result of this practice". So Jenner accurately predicted the eradication of smallpox some 175 years later using the technique he had discovered. There are no words with which adequately to do justice to his remarkable foresight. However, Jenner must have taken his observation in James Phipps, the boy he vaccinated with material from a cowpox lesion and then repeatedly challenged with material from smallpox lesions and multiplied it in his head by the number of people living on the planet. Even he could not have known then, what we know now, namely, that his vaccine and nearly all the others developed and widely used since can do much more than protect recipients against target infections. Setting aside the possibility of non-specific effects, which are beyond the scope of this chapter (see ► Chap. 1), vaccines can break the train of transmission of their target infections between humans, and so vaccinating just some people can be enough to protect everyone. In the cases of smallpox and more recently polio virus type 2, mass vaccination has led to eradication and thus protection for everyone who will ever live. No other advance in medicine comes anywhere close to this extraordinary power of vaccines.

The strategy adopted in the final phase of the eradication of smallpox in the 1970s reflects the growing understanding at the time that vaccinating people can also protect others. The very visible clinical features of smallpox made it relatively easy to recognise each individual case and then immunise around it, generating a ring of human immunity that the virus could not escape from. In fact many countries stopped universal smallpox vaccination long before global eradication had been achieved. Thus vaccine supplies could be used exclusively in areas where the infection was still circulating. Ring vaccination reappeared recently in the context of the Ebola epidemic in West Africa.

2.2 Why Direct Protection and Indirect Protection Are Not the Same Thing

It is easy to fall into the trap of thinking that direct and indirect protection afforded by vaccines are both one and the same thing. Immunise James Phipps and he will not get smallpox. That he will also therefore not infect his brother seems simply an inevitable consequence of the protection he got from the vaccine himself. To demonstrate that it is not as simple as that, it is worth considering the example of developmental "transmission-blocking" malaria vaccines. Given to humans, these consist of antigens expressed by the malaria parasite only during the stages of its life cycle when it is resident in the mosquito. When the insect takes a blood meal from an immunised human, it ingests not only malaria parasites but also vaccine-induced antibodies, which bind to them as they develop inside the insect reducing their viability and thus affording protection to the human providing the mosquito's next blood meal. The altruism inherent in such vaccines creates problems for their licensure as regulation of medicines is driven by considerations of safety and of benefit to the recipient, not others. For these vaccines in particular, but actually for most other vaccines as well, we need a new developmental paradigm that recognises that they really work for the common good and need to be deployed towards that end to achieve maximum impact and cost benefit.

Of course the concept of indirect protection – previously often referred to as "herd immunity" – is not novel. Implicit in long-standing advice to attain and then maintain

95% (and not 100%) coverage with measles-containing vaccine was the recognition that while there would always be some who would not receive or make protective responses to the vaccine, disease control for all could nevertheless be achieved, even for an infection as contagious as measles. However the ubiquitous nature of such effects among the vaccines used in universal programmes (tetanus – acquired from soil bacteria, not other people, being the one unequivocal exception) and the dominance of such effects in ensuring the effectiveness of many programmes have only become evident more recently. Indirect effects are no longer considered a "bonus extra" but are understood to be at the core of how vaccines impact on disease and, to an increasing extent, they drive the design of the programmes used – the numbers of doses of vaccines given and the ages of the recipients.

2.3 Immunising Teenagers and Protecting Everyone Against Meningococci

The recent history of the deployment of conjugate meningococcal vaccines in the UK is a particularly informative example of this. In the 1990s, in the wake of the successful introduction of conjugate vaccines against *Haemophilus influenzae* type b, several protein-polysaccharide conjugate vaccines against *Neisseria meningitidis* capsular group C were developed. A rapid rise in the number of severe and fatal cases of meningitis and septicaemia had been occurring in the UK during that decade due to spread of a hyperinvasive strain (clonal complex (cc) 11) bearing this capsule, both in young children and teenagers. The target of the rolling programme introduced in late 1999 was infants who received three doses of vaccine, while a one-off "catch up" programme offering vaccine to all children up to the age of 20 years was also rapidly implemented with the aim of preventing cases in older age cohorts. The licensure of the vaccines was based upon their ability to induce serum bactericidal antibody. From this, it was inferred that they would protect recipients against invasive disease. Between 2009 and 2015, a very similar epidemic of hyperinvasive cc11 meningococcal disease was detected, this time expressing group W capsule. Once again the UK authorities acted rapidly and decisively to attempt to control the epidemic using conjugate vaccines. However the strategy used was entirely different. This time infants and young children were not immunised at all – despite the availability of licenced vaccines and the fact that severe cases were being seen in this age group. Instead vaccination has been targeted exclusively at teenagers – the age group among whom upper respiratory tract carriage of meningococcus is most prevalent. In the 15 years between the two interventions, it had become clear that conjugate meningococcal vaccines actually work at the population level by eliminating the circulation of hypervirulent strains among the target capsular group(s) of the vaccine(s) used. Infants and young children may have the highest risk of disease, but carriage is comparatively rare in this age group. By immunising adolescents, (in whom the vaccines also induce larger and more long-lasting responses than in young children), all age groups are indirectly protected (see ► Chap. 22).

2.4 Maternal Immunisation

Problems with control of pertussis by childhood immunisation have been an emerging concern since early in the twenty-first century. Development, licensure and adoption of acellular pertussis vaccines for infants and young children in many wealthier countries, alongside continued use of whole cell vaccines in others, both combined with diphtheria, tetanus and other antigens for infants, led initially to effective pertussis control (see ► Chap. 18). However the first decade of the twenty-first century saw new resurgences of disease in several acellular vaccine-using countries. Several lines of evidence suggest that pertussis vaccines in general and acellular vaccines in particular induce protection that is shorter lived and incomplete against onward transmission.

Pertussis presenting as chronic cough in adolescents and young adults has become more widely recognised, and transmission from these individuals to their newborn unimmunised infants can result in severe cases and deaths. The UK authorities responded to just such a resurgence in 2012 by offering vaccine to pregnant mothers. Subsequent case-screening and case-control evaluations of effectiveness have provided convincing evidence that this approach works and many other countries have now followed suit (see ▶ Chap. 6). Protecting infants by immunising their mothers is, again, nothing new, having been used to prevent neonatal tetanus for many years in poorer settings where this is a significant public health problem. It has also been an observed benefit of maternal influenza immunisation programmes implemented to protect pregnant women at high risk from flu. Its success and widespread acceptance as a means to prevent pertussis is likely to accelerate development of similar programmes using developmental maternal vaccines against other severe neonatal infections including group B *Streptococcus* and respiratory syncytial virus (see Part IV).

2.5 Indirect Effects of Influenza Vaccines in Healthcare Workers and Children

Over the many years they have been available, the vast majority of seasonal influenza vaccine use in most countries has aimed at direct protection of recipients. Every autumn, large numbers of doses are earmarked for elderly people and patients with a range of chronic disorders, all deemed to be at high risk of severe or fatal flu infection. Even if high coverage rates are achieved, which is unusual, this approach cannot be expected to impact significantly upon flu circulation in the population at large as transmission occurs in all age groups and particularly in childhood. However, one aspect of traditional flu vaccine use does aim higher than simple prevention of morbidity in recipients and that is immunisation of healthcare workers (HCWs). Hospitals are subject to major seasonal fluctuations in workload due to wintertime epidemics of respiratory and gastrointestinal viruses. Staff are continuously exposed and often infected. Two serious adverse consequences are that they then infect other vulnerable patients and that they may be absent from work during their illnesses reducing the capacity to deliver healthcare at times of peak demand. Immunisation of HCWs against flu has the potential to reduce these problems and is actively promoted in many settings. Given that there is good quality evidence that – at least when there is a good match between the vaccine and circulating strains – flu vaccines prevent flu in healthy adults and can also prevent onward transmission in some settings, this policy, designed to protect the function of the health service and to reduce flu morbidity and mortality among its patients as well as its employees, makes good sense. However, evidence that this approach actually delivers on these endpoints in the healthcare setting is surprisingly weak. This undermines the argument that such immunisation should be mandatory as, for example, it commonly is for hepatitis B vaccine. In addition, studies that suggest that repeated annual doses of inactivated flu vaccine may result in progressive falls in immunogenicity and effectiveness suggest that other strategies may be needed to tackle this problem.

There is emerging evidence that annual universal childhood immunisation against influenza using live attenuated intranasal vaccine (LAIV) could be an effective approach to population-wide influenza control. The UK started offering universal one-dose LAIV for 2- and 3-year-old children in 2014 and has progressively raised the upper age limit in successive years. Ecological data support the idea that preventing flu in young children reduces the incidence of influenza-like illness in other age groups, and, most recently, 2015–2016 data from Scotland and Northern Ireland, where the programme was implemented more effectively with higher coverage and across a wider age range, show that the incidence never crossed the epidemic threshold, unlike England and Wales where fewer children were immunised. This apparent success is bolstered

by early supportive data from Canada and Finland with the nasal vaccine in children. However, recent data from the USA has failed to demonstrate effectiveness, particularly against the H1N1 strain, which has led to removal of the recommendation to use LAIV vaccine there in 2016 (see ► Chap. 14).

However, the indirect effects of childhood flu vaccination may extend further than prevention of flu in the wider population. Serious bacterial infections, including those caused by pneumococcus and meningococcus, have been associated epidemiologically with influenza, and potential pathogenic mechanisms are well described. These observations hint that preventing bacterial infections may turn out to be as effectively done using vaccines against viruses, including flu, as by using vaccines targeted at the bacteria.

2.6 Indirect Protection Against Covid-19

Covid-19 is a respiratory infection with systemic symptoms. Immunity may be like that after "old" respiratory coronaviruses such as 229E and OC43, i.e. not very long-lasting. One example is the city of Manaus which was hit hard in 2020 with 80–90% of the population being infected. In 2021 with a new wave and a new variant of Covid-19 in Brazil, many were reinfected and there were again deaths. It is unlikely that vaccine-induced immunity would be better or last longer than after disease. In both cases, emergence of new variants of SARS-CoV-2 will pose a challenge for any immune population, with natural or vaccine-induced immunity.

So far there are few examples of population-level vaccination. In the USA with more than the third of the population being vaccinated, Covid-19 is still increasing in most states. The UK with almost 50% coverage is doing better; the effect of vaccinations is combined with an almost total lockdown. In Israel with over 50% of the total population and 90% of the 70-year-old being totally vaccinated, there is a great reduction of new Covid-19 cases, some of which may be attributed to breakage of transmission chain, i.e. herd immunity. This does not mean a permanent herd immunity, but more likely the unvaccinated people in the population remain susceptible to infections that are carried into the country.

To reach coronavirus-free state in an area or country, a vaccine coverage of 80–90% may be needed, taking into consideration the more infectious variants and the vaccine effectiveness lower than 90%. This by necessity will mean vaccinating children, at least from a certain age up. Still such a society will not be fully protected from infections coming from outside. Such newly introduced infections are likely to cause at least small outbreaks. New SARS CoV-2 variants that evade even if partly, vaccine-induced immunity will pose a greater threat. Therefore, a herd immunity in a population will remain volatile, and periodical revaccinations are likely to be required.

Further Reading

Campbell H, Saliba V, Borrow R, Ramsay M, Ladhani SN. Targeted vaccination of teenagers following continued rapid endemic expansion of a single meningococcal group W clone (sequence type 11 clonal complex), United Kingdom 2015. Euro Surveilli: bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2015;20(28).

Cartwright KA, Jones DM, Smith AJ, Stuart JM, Kaczmarski EB, Palmer SR. Influenza A and meningococcal disease. Lancet. 1991;338(8766):554–7.

Dabrera G, Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, et al. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012–2013. Clin Infect Dis. 2015;60(3):333–7.

Didierlaurent A, Goulding J, Patel S, Snelgrove R, Low L, Bebien M, et al. Sustained desensitization to bacterial Toll-like receptor ligands after resolution of respiratory influenza infection. J Exp Med. 2008;205(2):323–9.

Febrer M, McLay K, Caccamo M, Twomey KB, Ryan RP. Advances in bacterial transcriptome and transposon insertion-site profiling using second-generation sequencing. Trends Biotechnol. 2011;29(11):586–94.

Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, et al. Efficacy and

effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola ca Suffit!). Lancet. 2017;389(10068):505–18.

Henderson DA. Principles and lessons from the smallpox eradication programme. Bull World Health Organ. 1987;65(4):535–46.

Hodgson D, Baguelin M, van Leeuwen E, Panovska-Griffiths J, Ramsay M, Pebody R, et al. Effect of mass paediatric influenza vaccination on existing influenza vaccination programmes in England and Wales: a modelling and cost-effectiveness analysis. Lancet Public Health. 2017;2(2):e74–81.

Jenner E. On the origin of the vaccine inoculation. London: D N Shury; 1801.

Klugman KP, Chien YW, Madhi SA. Pneumococcal pneumonia and influenza: a deadly combination. Vaccine. 2009;27(Suppl 3):C9–C14.

Ladhani SN, Beebeejaun K, Lucidarme J, Campbell H, Gray S, Kaczmarski E, et al. Increase in endemic Neisseria meningitidis capsular group W sequence type 11 complex associated with severe invasive disease in England and Wales. Clin Infect Dis. 2015;60(4):578–85.

Loeb M, Russell ML, Moss L, Fonseca K, Fox J, Earn DJ, et al. Effect of influenza vaccination of children on infection rates in Hutterite communities: a randomized trial. JAMA. 2010;303(10):943–50.

Lu YJ, Gross J, Bogaert D, Finn A, Bagrade L, Zhang Q, et al. Interleukin-17A mediates acquired immunity to pneumococcal colonization. PLoS Pathog. 2008;4(9):e1000159.

McLean HQ, Thompson MG, Sundaram ME, Meece JK, McClure DL, Friedrich TC, et al. Impact of repeated vaccination on vaccine effectiveness against influenza A(H3N2) and B during 8 seasons. Clin Infect Dis. 2014;59(10):1375–85.

Mina MJ, Metcalf CJ, de Swart RL, Osterhaus AD, Grenfell BT. Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality. Science. 2015;348(6235):694–9.

Nunes JK, Woods C, Carter T, Raphael T, Morin MJ, Diallo D, et al. Development of a transmission-blocking malaria vaccine: progress, challenges, and the path forward. Vaccine. 2014;32(43):5531–9.

Pebody RG, Green HK, Andrews N, Boddington NL, Zhao H, Yonova I, et al. Uptake and impact of vaccinating school age children against influenza during a season with circulation of drifted influenza A and B strains, 4th ed. England, 2014/15. Euro Surveilli. 2015;20(39): Article 4.

Thomas RE, Jefferson T, Demicheli V, Rivetti D. Influenza vaccination for healthcare workers who work with the elderly. Cochrane Database Syst Rev. 2006;(3):CD005187.

Thorrington D, Jit M, Eames K. Targeted vaccination in healthy school children – can primary school vaccination alone control influenza? Vaccine. 2015;33(41):5415–24.

Thors V, Morales-Aza B, Pidwill G, Vipond I, Muir P, Finn A. Population density profiles of nasopharyngeal carriage of 5 bacterial species in pre-school children measured using quantitative PCR offer potential insights into the dynamics of transmission. Hum Vaccin Immunother. 2016;12(2):375–82.

Childhood and Adolescent Immunization Programs in Europe

Pierre Van Damme

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_3

3

3.1 Introduction

In 2005, the World Health Assembly adopted resolution WHA58.15 on global immunization strategy. It "urged Member States to meet immunization targets expressed in the United Nations General Assembly special session on children; to adopt the Strategy as the framework for strengthening of national immunization programmes, with the goal of achieving greater coverage and equity in access to immunizations, of improving access to existing and future vaccines, and of extending the benefits of vaccination linked with other health interventions to age groups beyond infancy; to ensure that immunization remains a priority on the national health agenda, …."

The diversity of the European Region is reflected not only in the cultures and languages but also by economies and health systems. The economic, cultural, and historical differences have all contributed to the resulting diversity seen in the health systems and health governance among them, differences that have contributed to the wide variation of immunization programs currently in place.

All Member States of the European Union and a large number of the non-EU countries in the WHO European Region have a national immunization technical advisory group (NITAG) on immunization, and most of these NITAGs have a legislative basis for making recommendations to the government (i.e., the Ministry of Health). The effect of the recommendations varies according to how immunization programs are organized (centralized or decentralized) and the balance between public and private sector provision of services. In countries such as Belgium, Germany, and Spain, the communities (Belgium), the Länder (Germany), or the "autonomous regions" (Spain) have the responsibility for prevention and protection of public health. Although each country has a NITAG, its recommendations can be applied differently at the local level, and the vaccines actually provided depend on the choice of private practitioners and reimbursement arrangements with insurance companies, or on the (de)centralized public policy of the (local) government.

Immunization policy or practice has not been subject to European legislation for harmonization, although many relevant processes such as batch release are controlled through EU legislation.

The vaccines and immunization schedules used in the 53 countries of the WHO European Region are undergoing continuous change, with the introduction of new antigens and the increasing use of combined antigen vaccines and simplified schedules with a lower number of vaccine doses. Annual information is collected from WHO Member States on immunization programs and vaccine-preventable diseases using the WHO/UNICEF joint reporting form. This information can easily be consulted through the WHO website at: ► http://apps.who.int/immunization_monitoring/globalsummary/schedules. ECDC offers a *Vaccine Scheduler* tool; it is an interactive platform of *vaccination schedules* for individual European countries and specific age groups (► http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx).

Country immunization schedules can be consulted by vaccine or target disease, or compared with each other.

3.2 Childhood Vaccination

In Europe, childhood vaccination is offered through routine immunization programs at "well-baby" clinics, through the private sector (general practitioners or pediatricians), or through a combination of both public and private sector.

The current childhood immunization schedules for vaccination below 24 months of age in the EU countries can be divided into four major groups for the infant vaccination schedule:

- **Group 1**

Early-onset 3 plus 1 schedule with vaccination at 2, 3, and 4 months of age (Bulgaria, Germany, Hungary, Luxemburg, Malta, and Belgium using timings of 8, 12, and 16 weeks) or the schedule similar to that of the USA of 2, 4, and 6 months of age (Croatia, Cyprus,

Greece, Ireland, Latvia, Liechtenstein, Lithuania, Poland, and Portugal), all followed by a fourth dose in the second year of life.

- **Group 2**

Early onset according to a 2 plus 1 schedule, with vaccination at 2 and 4 months, followed by a third dose at 11 months (France, Romania, Slovakia, and Spain).

- **Group 3**

Late-onset 2 plus 1 schedule with vaccination at 3 and 5 months of age followed by a third dose at 12 months of age (Austria, Czech Republic, Denmark, Finland, Iceland, Italy, Norway, Slovenia, Sweden, and the Netherlands).

- **Group 4**

Late-onset 3 plus 1, starting at the age of 3 months (Estonia), with a fourth dose in the second year of life.

Only one or two countries use only a three-dose primary immunization schedule with no penta- or hexavalent booster in the second year of life. In the remaining WHO European Region countries, the Extended Program of Immunization (EPI) schedule is often implemented together with primary infant immunization offered at 6, 10, and 14 weeks – in some countries followed by infant booster immunization.

The various childhood immunization schedules in Europe evolved historically, taking into consideration the local vaccine-preventable infection epidemiology, and were based on the experiences gained from immunization with whole-cell pertussis-containing diphtheria–tetanus–pertussis (DTP) vaccines (2-, 3-, 4- and 2-, 4-, 6-month schedules), where the need for three doses was shown. The 3- and 5-month schedule, on the other hand, evolved from the vaccination priming schedule for the diphtheria–tetanus (DT) vaccine, which was introduced first in Italy in 1981 and in Sweden in 1986. That schedule was maintained in a number of countries when a pertussis vaccine was added to DT.

The four different schedules used in Europe have been shown to accomplish their primary goal, i.e., to induce rapid protection and immunological memory against the vaccine-preventable infections targeted by the immunization, in close to 100% of vaccinated infants. By starting at 2 months of age (or 8 weeks, which offers a smaller range than 2 months), protection will be achieved 1 month earlier than with a 3-, 4-, and 5-month schedule or 3- and 5-month schedule.

A measurable antibody response does not develop in all children after the priming doses, and the level of the antibody responses may be low. The booster dose will induce measurable antibody responses in almost 100% of children and result in much higher antibody levels than after the priming doses.

European vaccination schedules all call for at least one or two booster doses between the ages of 2 and 18 years, but with quite a variation in local schedules. Such a variation creates issues for migrating families, as parents and physicians have to face difficult decisions on how to adapt or complete vaccination schedules when families move from one European country to another.

3.3 Adolescent Vaccination

Vaccinating adolescents offers three types of immunization opportunities: catch-up on missed vaccinations, boosting waning immunity (derived from previous childhood vaccinations such as for pertussis), and the achievement of primary immunization through administration of new vaccines best delivered during adolescence (e.g., meningococcal and human papillomavirus vaccines; ◘ Table 3.1). In the future, adolescence may also be the target age range for administration of some vaccines currently in development.

Adolescent vaccination can prevent considerable morbidity in adolescent and adult age groups and limit the spread of infectious diseases in the population. In Europe, adolescent vaccination can be provided through routine immunization programs or campaigns, run with the support and participation of either the private sector or the public sector, or both. Vaccines can be administered through clinic-based schemes (e.g., in health centers),

Table 3.1 Examples, advantages, and disadvantages of adolescent vaccination strategies (Brabin et al. 2008)

Vaccine implementation			
Strategy	Example vaccine	Advantages for adolescent programs	Disadvantages for adolescent programs
Universal	Meningococcal conjugate (MCV4)	Increased likelihood of achieving herd immunity	The ability to achieve herd immunity is undermined if low vaccination rates occur
		Decreased likelihood of inducing stigma around certain diseases such as sexually transmitted infections	Higher costs to society
Targeted	Hepatitis B virus (HBV)	Reduced costs if every adolescent does not require vaccination	Target groups can be difficult to identify
			Adolescents may not perceive themselves to be high risk
		Reduced risk of adverse events in the whole population	Adolescents may be unwilling to seek care if fear of judgment or lack of confidentiality exists, especially for sexually transmitted infections
			Increased risk of stigmatization, particularly for sexually transmitted infections
School-based	Rubella (MMR, MR, or R)	In countries with school-based programs, success has been mediated by the requirement to attend school and by a lack of private sector healthcare	School attendance by adolescents is low in many countries
			School-based healthcare infrastructure is generally directed at younger children; therefore, retention and/or creation of appropriate infrastructures in many countries need to be developed to create an adolescent program
			Future adolescent vaccines targeted at sexually transmitted diseases necessitate integration with health promotion; in particular, sexual health issues associated with absenteeism require development of catch-up programs
Catch-up	Pertussis (Tdap)	Maintain immunity to prevent infection and subsequent infection of un-immunized individuals	Timing of catch-up programs needs to coincide with other preventive services to increase the likelihood of vaccination uptake
		Reduced healthcare costs associated with decreased disease burden	

Table 3.1 (continued)

Vaccine implementation			
Mass vaccination	Typhoid fever (Ty21a, Vi)	Large number of individuals can be vaccinated within a rapid timeframe	Suitable for single-dose vaccinations; however, less effective for multi-dose vaccines, as the likelihood of individuals returning for subsequent vaccination decreases with each additional dose
		Excellent for outbreak situations	
		Limited amount of resources can be mobilized	

in the community, or in schools. Mixed systems of school health and private sector can offer benefits, but require coherence, coordination, and good communication between all parties.

However, because of the age of the target group – the WHO definition of an adolescent being aged between 10 and 19 – legal issues arise: parental consent, minors' consent (assent) and legality thereof, the concept of "capacity to understand" and "competence," and action in case of parental opposition. Another feature that emerges is the disconnect between the practice of immunization and other medical procedures ("treatment"), including the role of school health services in dealing with other health problems, such as drug use, alcohol use, and violence.

Furthermore, medical issues in this age range also complicate the matter of immunization; a substantial proportion (about 10%) of young people suffer from chronic illnesses (e.g., diabetes, whose incidence in young people is increasing) that need to be considered before vaccination is given. Other temporal, coincidental associations in adolescents, e.g., asthma, autoimmune thyroiditis, and Guillain–Barré syndrome may raise safety concerns.

In Europe, as for the implementation of the childhood immunization program, the adolescent program differs by country and sometimes by state, region, or canton and involves the public and/or private sectors.

In general, in Europe, adolescent immunizations lag behind childhood uptake figures, in particular for the second dose of measles, mumps, and rubella vaccine, the booster dose of the pertussis vaccine, or the uptake of human papillomavirus vaccines. Waning immunity or absence of immunity in adolescents makes them reservoirs of infection, with transmission possibilities to other age groups in the population. In many countries, adolescents are an underserved group that is hard to reach because of their good health and sparse preventive medicine visits.

Studies among adolescents have identified risk factors associated with suboptimal immunization, which may include financial and logistic constraints, in addition to parental and adolescent knowledge and beliefs: e.g., socioeconomic status, lack of medical insurance, large family size, divorced parents, foreign nationality, and language barriers.

School health services have been identified as playing a specific role in the prevention and response to adolescent health problems (Table 3.2). Where there were no strong school health facilities or vaccine programs, such as in France, Germany, and Italy, rates of adolescent vaccination have been low. With school attendance mandatory for high proportions of adolescents in Europe, the

Table 3.2 School health system per country: vaccine type and school health system

Country	Coverage	Vaccine	School health system
Belgium	>68–75%	Hepatitis B	Present
Croatia	>93%	Hepatitis B	Present
Finland	Estimated 95%	Not specified	Present
France	35–95%	Not specified	No longer existing since 1998
Germany	Low coverage in adolescents	Not specified	Not present
Greece	18–45%	Not specified	Not present
Hungary	>99%	Not specified	Present
Italy	>90%	Hepatitis B	Present
Norway	90–92%	Not specified	Present
Slovenia	92–99%	Not specified	Present
The Netherlands	>90%	Not specified	Present
Turkey	85–98%	Not specified	Present

Adapted from FitzSimons et al. (2007)

presence of a captive audience makes vaccination at school feasible. Benefits of school health programs (besides high coverage rates) include easy access to vaccination for parents (no effort required from them) and easy monitoring of coverage and side effects. On the down side, school immunization programs form only one part of a school medicine system and cannot manage common adolescent problems including smoking, alcohol and drug use, sexual behavior, and violence, unless it is fully embedded in a comprehensive program. In addition, communication with parents is indirect, which can raise some legal issues.

The introduction of a centralized immunization information system (enabling recording, recall, and informing healthcare workers and parents), the organization of a school health program, offering the vaccine free of charge, and the implementation of school-entry mandates have been recognized as factors that could contribute to improved vaccination coverage in adolescents. In addition, advocacy and educational initiatives for parents, adolescents, and vaccinators should help to support these programs and safeguard the health of adolescents.

The concept of promoting health in schools seems to be successfully taking off, but healthcare providers alone cannot meet adolescents' needs: there has to be a partnership and networking of vaccinators, teachers, parents, and young people all playing a role. Vaccination should be integrated into other interventions in health systems (e.g., sexual health education and sports medical examinations). Various approaches are currently being successfully used by different countries to reach adolescents.

3.4 Vaccination of Refugees and Immigrants

Since 2011, Europe has been facing one of the greatest migration inflows in its history: during 2011, there were an estimated 1.7 million immigrants into the EU from countries outside the

EU. According to Eurostat, after the Northern African turmoil, in 2012, EU countries received 300,000 asylum applications, which peaked at 1,300,000 in 2015, after the Syrian conflict and almost double the previous great migration inflow recorded in 1992, after the crisis in the former Yugoslavia. The UNHCR estimated that, in 2015, more than one million migrants arrived in Europe after crossing the Mediterranean Sea. Refugees and immigrants often come from countries in which poverty-related diseases are endemic, with disrupted healthcare systems and consequently a fall in vaccination coverage. This explains why they are at a high risk of vaccine-preventable diseases, not to mention the risky conditions they endure during the journey to Europe (unsanitary conditions, overcrowding).

Overall, migrants and refugees have lower immunization rates than European-born individuals, with children being at a higher risk of being unvaccinated against measles, mumps, and rubella (MMR; ◘ Table 3.3). The coverage for the oral polio vaccine has been estimated to be less than 15% among Syrian children refugees in Germany.

In 2016, the WHO, UNICEF, and UNHCR officially stated that migrants, asylum seekers, and refugees should have nondiscriminatory and equitable access to vaccinations. They recommended vaccinating these populations; avoiding delays, in accordance with the immunization schedule of the host country; and offering documentation of administered vaccines to avoid duplications.

However, access to complete vaccination is difficult to ensure: migrants are moving throughout Europe, whereas vaccines must often be given in consecutive doses; information on the immunization status of the migrants is often lacking; recommended immunization schedules differ among EU countries complicating the catch-up programs; a number of the host countries face severe economic crises, challenging migrants' access to the local healthcare services; migrants may refuse registration by medical authorities for the fear of legal consequences; a lack of coordination among EU public health authorities may cause either a lack of vaccine administration or duplication.

Although migrants have the right to healthcare under legal settlements issued by the EU, there is no standard European approach for offering healthcare to migrants. Each country has its own policy.

To overcome many of these issues at the EU or country level, the WHO proposes tailoring immunization services to the specific needs of the target population, to strengthen social mobilization, advocacy, and communication toward these specific populations, to develop electronic vaccination registries, and to introduce coordination among public health authorities of EU countries.

In general, the vaccination status of migrants and refugees arriving in Europe should first be assessed through documentation; when this is lacking, they should be regarded as unvaccinated and should then be vaccinated according to the local recommended schedule. Catch-up immunization programs should prioritize MMR and inactivated poliovirus vaccines, followed by the DTP vaccines and hepatitis B vaccine (depending on the age after first screening). Vaccination against polio should be considered a high priority for migrants coming from countries in which polio is endemic. In 2016, some countries or regions (e.g., Flanders) started to offer asylum seekers polio (when indicated), MMR and diphtheria, tetanus, and acellular pertussis vaccination (for pregnant women) immediately on entry into the country, with further follow-up of the immunization in the respective centers for asylum seekers. Recently in a number of EU countries (e.g. Belgium) also COVID19 vaccines are offered to refugees and saylum seekers.

Clearly, under-immunization and therefore susceptibility to vaccine-preventable infections pose a risk to the health of migrants and refugees and, in turn, can result in epidemics in the host country.

Table 3.3 Immunization coverage (in %) for 2014, according to the estimates of the WHO and UNICEF for six of the most frequent countries of origin of migrants arriving in Europe (2012), compared with five EU countries (Mipatrini et al. 2017)

Vaccine	Code	Syria	Iraq	Afghanistan	Albania	Pakistan	Eritrea	Italy	Greece	Germany	Denmark	Sweden
Bacillus Calmette–Guerin	BCG	81	95	86	99	85	97	–	–	–	–	–
Diphtheria–tetanus–pertussis first dose	DTP1	65	77	82	99	79	97	98	99	98	96	99
Diphtheria–tetanus–pertussis third dose	DTP3	43	64	75	98	72	94	94	99	96	94	98
HBV third dose	HepB3	71	62	75	98	72	94	94	96	87	–	53
HBV birth dose	HepB_BD	78	43	4	99	–	–	–	–	–	–	–
Haemophilus influenzae third dose	Hb3	43	64	75	98	72	94	94	99	94	94	98
Measles-containing vaccine first dose	MCV1	54	57	66	98	61	96	86	97	97	90	98
Measles-containing vaccine second dose	MCV2	49	57	39	98	52	–	–	83	92	84	95
Maternal immunization with ≥2 doses of tetanus toxoid	PAB	92	72	70	92	75	94	–	–	–	–	–
Pneumococcal conjugate vaccine	PCV3	–	–	40	99	72	–	55	96	69	93	97
Polio vaccine third dose	Pol3	52	67	75	98	72	94	94	99	95	94	98
Rotavirus	RotaC	–	29	–	–	–	25	–	–	–	–	–

Bibliography

Bearinger LH, Sieving RE, Ferguson J, Sharma V. Global perspectives on the sexual and reproductive health of adolescents: patterns, prevention, and potential. Lancet. 2007;369(9568):1220–31.

Brabin L, Greenberg DP, Hessel L, Hyer R, Ivanoff B, Van Damme P. Current issues in adolescent immunization. Vaccine. 2008;26(33):4120–34.

ECDC. Scientific panel on childhood immunisation schedule: diphtheria-tetanus-pertussis (DTP) vaccination – report. European centre for disease prevention and control, Stockholm. 2009, 40p.

FitzSimons D, Vorsters A, Hoppenbrouwers K, Van Damme P, Viral Hepatitis Prevention Board (VHPB), European Union for School and University Health and Medicine (EUSUHM). Prevention and control of viral hepatitis through adolescent health programmes in Europe. Vaccine. 2007;25(52):8651–9.

Keane MT, Walter MV, Patel BI, et al. Confidence in vaccination: a parent model. Vaccine. 2005;23(19):2486–93.

Kleinert S. Adolescent health: an opportunity not to be missed. Lancet. 2007;369(9567):1057–8.

Kpozehouen E, Heywood AE, Kay M, Smith M, Paudel P, Sheikh M, MacIntyre CR. Improving access to immunisation for migrants and refugees: recommendations from a stakeholder workshop. Aust N Z J Public Health. 2016;41(2):118–20.

Mipatrini D, Stefanelli P, Severoni S, Rezza G. Vaccinations in migrants and refugees: a challenge for European health systems. A systematic review of current scientific evidence. Pathog Glob Health. 2017;111(2):59–68.

Reyes-Uruena JM, Noori T, Pharris A, Jansà JM. New times for migrants' health in Europe. Rev Esp Sanid Penit. 2014;16(2):48–58.

Rosenthal SL, Kottenhahn RK, Biro FM, Succop PA. Hepatitis B vaccine acceptance among adolescents and their parents. J Adolesc Health. 1995;17(4):248–54.

Sakou I-I, Tsitsika A, Papaevangelou V, Tzavela E, et al. Vaccination coverage among adolescents and risk factors associated with incomplete immunization. Eur J Pediatr. 2011;170:1419–26.

Vandermeulen C, Roelants M, Theeten H, et al. Vaccination coverage and sociodemographic determinants of measles-mumps-rubella vaccination in three different age groups. Eur J Pediatr. 2008;167:1161–8.

Wallace LA, Young D, Brown A, et al. Costs of running a universal adolescent hepatitis B vaccination programme. Vaccine. 2005;23:5624–31.

Williams GA, Bacci S, Shadwick R, Tillmann T, Rechel B, Noori T, Suk JE, Odone A, Ingleby JD, Mladovsky P, Mckee M. Measles among migrants in the European Union and the European economic area. Scand J Public Health. 2016;44(1):6–13.

Wilson TR, Fishbein DB, Ellis PA, Edlavitch SA. The impact of a school entry law on adolescent immunization rates. J Adolesc Health. 2005;37(6):511–6.

Zimet GD, Liddon N, Rosenthal SL, Lazcano-Ponce E, Allen B. Psychosocial aspects of vaccine acceptability. Vaccine. 2006;24(Suppl 3):S201–9.

Vaccine Hesitancy, Acceptance, and Demand

Robb Butler

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_4

4

4.1 Background

The World Health Organization defines vaccine hesitancy as "…a delay in acceptance or refusal of vaccines despite the availability of vaccination services. Vaccine hesitancy is complex and context specific varying across time, place and type of vaccine." The hesitancy continuum extends from those that accept all vaccines, but are unsure about their decisions for some or all vaccines, through to those who refuse all vaccines, but are unsure about these decisions (Fig. 4.1). In that sense, hesitancy affects demand and is most closely associated with negative demand. Addressing vaccine hesitancy requires an understanding of the magnitude and setting of the problem, diagnosis of the root causes, tailoring strategies based on local evidence to address the causes, evaluation to gauge if the intervention has been successful in improving vaccine acceptance, and monitoring.

In March 2012, the Strategic Advisory Group of Experts (SAGE) on immunization established a working group to define vaccine hesitancy and its scope and provide advice on how to address vaccine hesitancy, including a landscape analysis of stakeholders working on the issue and identifying promising practices. It presented its work to SAGE at the WHO premises in Geneva, in October 2014 (▶ http://www.who.int/immunization/sage/meetings/2014/october/1_Report_WORKING_GROUP_vaccine_hesitancy_final.pdf), and shortly thereafter published a supplement in *Vaccine* in August 2015. Later that same year, an informal working group was established to develop an understanding of "demand" (definition, components, actors, and determinants) and to explore the means of measuring progress on improving demand. The informal working group has been instrumental in building consensus and understanding around the term demand and its determinants, sharing promising practices from around the globe and considering the best approaches and methods to measuring demand and the impact of demand-generating initiatives. For the purposes of this chapter, we align with the hesitancy and demand working groups' definitions and understanding of demand – considering hesitancy and acceptance as factors of demand. We focus primarily on hesitancy, its scope and expression in the European Region,

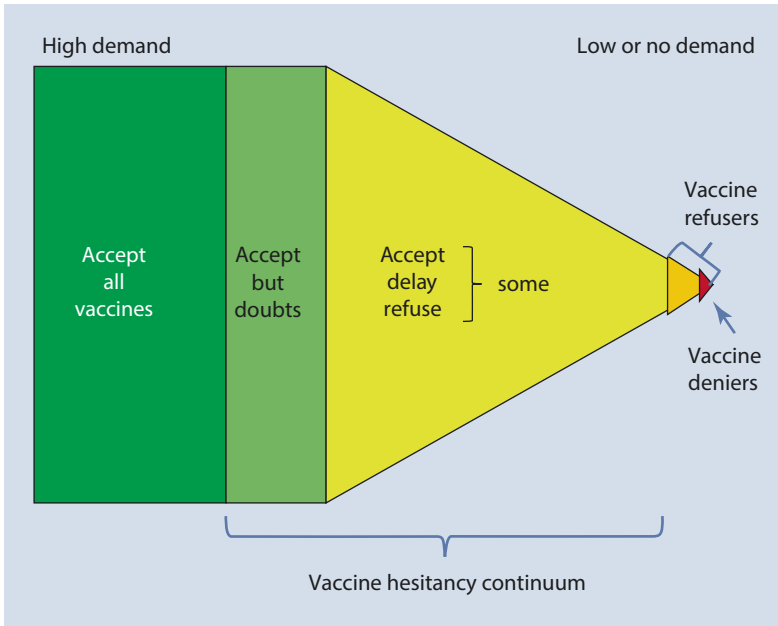


Fig. 4.1 History of vaccine acceptance in Europe. Noni Mac Donald, ▶ www.sabin.org/sites/sabin.org/files/1-vaccine_hesitancy_final_draft_7_jan26_2017.pdf

and strategies to address it from a program planning and an individual (provider–parent/patient) perspective.

Figure 4.1 demonstrates the spectrum of demand and the effect of vaccine hesitancy.

In Europe, program organizers have become acutely aware of the potential damage and threat that vaccine hesitancy, public mistrust of vaccines and immunization services, and the rejection of vaccines pose. It is unclear whether vaccine hesitancy and associated risks have increased within the European public over recent years (as some observers suggest) or whether, instead, vaccination programs have become more sensitive and aware of the phenomena as they attempt to reach remaining under-immunized populations and meet ambitious coverage targets and disease control goals.

Vaccine hesitancy is not a new phenomenon. Following the introduction of small pox immunization, as early as the mid-1800s, hesitancy and vaccine objection have been documented in Europe. In the UK, the smallpox vaccination induced fear and protest: some believing that the practice of inoculation was un-Christian and others skeptical of Edward Jenner's ideas or objecting on the grounds that the practice violated their personal liberty (mandatory vaccination for infants up to 3 months of age was introduced in 1853). At that time, anti-vaccination lobbies or "leagues" were established with their own journals and communication materials.

A resurgence and lingering of vaccine-preventable diseases such as measles, rubella, diphtheria, and pertussis, resulting in hospitalization and deaths of infants, children, and adults over the past decade, have prompted renewed interest in understanding why Europe, a region rich in resources and capacity, has been unable to close the immunity gaps and meet regional disease control and elimination goals. Immunization service managers and administrators are, in turn, eager to better understand parent/patient hesitancy and health-seeking behaviors to appropriately motivate them to vaccinate and remove factors limiting their ability or opportunity to utilize immunization services. Member States of the European Region restated their commitment to immunization by adopting the European Vaccine Action Plan (EVAP) 2015–2020 in 2014, the first regional plan to openly acknowledge the extent of vaccine hesitancy, vaccine skepticism, and sub-optimal parent/patient demand for immunization services and need for vaccine trust. The EVAP second strategic objective calls for "individuals [to] understand the value of immunization services and vaccines and demand vaccination," and the third calls for "the benefits of vaccination (to be) equitably extended to all people through tailored, innovative strategies."

4.2 Shortcomings of Terminology

As a term, "hesitancy" has often been used synonymously and interchangeably with "lack of confidence" or "confidence-gap" by some academics and practitioners alike. However, in Europe its expression is multifaceted, including but not limited to trust in vaccines and/or the authorities that provide them. Attributing recent disease incidence and outbreaks in Europe to parental or provider confidence is arguable and may deflect attention from systemic and service delivery shortcomings by placing responsibility solely on the "hesitant" parent/patient. In this sense, the term should be used with caution. In Europe, other system side factors have contributed to disease burden. Even when demand is evident, there are factors that prevent action, despite an intention to vaccinate by a parent/patient. Demand for immunization services does not equate to immunization service utilization. Vaccine supply disruptions, economic/financial/societal crises, program delivery disruption or weaknesses (e.g., delayed introduction of a second dose of measles, or a period of health worker shortages), and poor-quality service delivery, including poor communication, for example, have all resulted in sub-optimal coverage and underutilization of vaccination services in Europe. Some of these factors continue to affect program reach, coverage, and utilization, particularly in countries challenged by high vaccine prices, lack of long-term secured domestic funding for their

programs, and unstable vaccine supply. Some countries, particularly those with weak infrastructures, have had to face the additional burden of addressing the migrant influx into Europe, many of whom also require immunization in addition to having other support needs.

4.3 Vaccination Complacency, Convenience, and Confidence in Europe

Vaccine hesitancy includes factors such as complacency, convenience, and confidence, each of which is exhibited at parent/patient, provider, and decision-making levels in Europe today.

In terms of convenience, parent/patients are not presented with opportunities to access immunization services outside traditional working hours and in locations other than health facilities. Very few countries have considered pharmacies as an option for immunization service delivery (Ireland and Portugal are the exceptions to this), despite strong evidence from the USA and Canada that influenza vaccine rates have been boosted by the use of pharmacies, mini-marts, and other nontraditional outlets, for many years now.

Immunizations can be unnecessarily stressful and anxious events for many children and adults who fear needles and the pain of immunization. This can lead to long-term nonadherence with recommended schedules, missed immunizations, and even a shunning of healthcare services in general. Very few programs have considered the negative impact of pain of immunization. Few have made efforts to improve provider and parent/patient knowledge and skills to mitigate stress and anxiety during immunization. There are evidence-based strategies including noninvasive methods such as liquid-jet injection or even distraction techniques with better positioning that can address this problem. New technologies such as microneedles also promise to not only minimize pain but potentially enable the delivery of services through nontraditional outlets using nonmedical personnel.

Many parents/patients in Europe have grown complacent about diseases that most communities have not seen in decades. Complacent individuals thus consider the risks of the vaccine to outweigh the risk of contracting the disease. In that sense, vaccines have become a victim of their own success. This even extends to healthcare providers where many have not seen, first-hand, diseases such as measles, rubella, diphtheria, and pertussis in their practice. Complacency is also evident in political decision-making, with many countries unable to secure domestic resources for their programs against competing health, economic, and security priorities. This is particularly apparent in countries that have not experienced outbreaks recently. The decision-making environment in these countries faces an additional dilemma as the direct and indirect costs of outbreaks have not been calculated and appropriately understood, thereby hampering adequate planning.

The overall confidence and trust in vaccine effectiveness and safety, and in the authorities that deliver them, are positive, but do vary across Europe. The proliferation of conflicting information, from multiple sources within and outside of the region, has challenged decision-making regarding parent/patient vaccine acceptance and eroded the value of and trust in provider-delivered advice and recommendations. The ability of a single anti-vaccine individual to influence the health seeking behavior of others, including the intention to vaccinate, is greater now than ever before. Indeed, such individuals who understand how new media platforms are leveraged effectively is often more influential and may even be perceived as being more trustworthy than a trained medical or public health professional. This phenomenon has damaged vaccine acceptance and trust in many European countries. In some extreme cases, a single vaccine opponent has been responsible for the suspension of a vaccine program or severely undermined vaccine acceptance and uptake (human papilloma virus, Denmark, 2014). At the extreme end of the demand/hesitancy spectrum are vaccine deniers who oppose vaccines for diverse rea-

sons, but are not open to a change of mind. In Europe, these very small groups are not organized into a cohesive, financed, coordinated body and therefore cannot be considered a "movement" or "lobby," as is more commonplace in the USA or in Australia, for example. Recent work to mitigate the negative influence of "vocal" vaccine deniers has been undertaken by the WHO in Europe with a guidance document and training program based on psychological research into persuasion, on research into public health, on communication studies, and on WHO risk communication guidelines.

Many immunization programs in the region have relied over the years on communication campaigns solely focused on addressing misconceptions and misinformation. These fail to decrease hesitancy and, in some cases, backfire entirely. To some degree, this can be attributed to a lack of understanding by the program organizers that informed individuals are not necessarily behaviorally responsive ones and that knowledge does not predict action, and as such, closing the information gaps through awareness campaigns does not address hesitancy, ensure demand, or guarantee utilization. Social copying and behavioral imitation are also manifest among parent/patients, which are largely seen to be beneficial in increasing and maintaining vaccination coverage but are also evidently having a negative impact by amplifying nonvaccination behavior and anti-vaccination sentiment.

4.4 Strategies to Address Hesitancy

4.4.1 Understanding the Target Population: Diagnosing Hesitancy

As demand, hesitancy, and acceptance are context-specific, and program and community resilience variable across Europe, it should be considered a prerequisite for a program to locally gauge and diagnose the factors influencing vaccination intentions, decisions, and behaviors, with participation of affected (under-immunized) communities. General public and subgroup attitudes, knowledge, and behaviors must be regularly monitored and assessed frequently, to be able to inform and tailor program delivery and response to match the needs of the target subgroups. Success in countering anti-vaccination sentiment and safety concerns depends on this in particular. By tracking patient/parent sentiment and behavior with the use of operational research (such as surveys or rapid assessments), the immunization program ensures that people and communities, not only diseases, are at the center of immunization systems and empowers people to take a more active role in their own health. Using WHO tools, behavioral insight studies have uncovered the reasons for lower vaccination uptake in Roma, migrant, Jewish ultra-orthodox, and anthroposophic communities and found that both vaccine hesitancy (individual) and inappropriate or insufficient service delivery (program) affect uptake in each of these communities. The application of such "insight" and social science techniques and methods in some European contexts clearly demonstrates how programs can adopt approaches to tailoring the extension of service delivery according to the needs of communities.

Alongside the importance of diagnosing vaccine hesitancy and demand determinants in any population group, in addition to a consideration of the factors and determinants previously noted in this chapter, we should consider evidence-informed strategies for addressing vaccine hesitancy and improving vaccine uptake from the program perspective and from the individual provider–parent/patient perspective. Some of the strategies covered in this section are adapted from MacDonald et al. (2018) and are considered appropriate options in the European Region.

4.4.2 Communications Planning

The primary demand indicator of EVAP measures the presence of a communications plan as a proxy for resilience and a signal of com-

munications and advocacy capacity. Crisis (outbreak and vaccine safety-related "events") and risk communication plans should be developed and tested by programs. The communication plans should adhere to best practice and the key principles of risk communications and be proactive in nature. Clear roles and responsibilities of vaccination programs and emergency communication tasks should be accounted for, including the costing and resourcing of immunization communication activities. Audiences should be clearly identified and multiple channels of communication and messages envisioned. Communication plans must be bidirectional with the immunization programs being sensitive to the values and incorporating the concerns of the target audience. The drafted messages should be tailored to fit the target audience and strengthen or reinforce individuals' understanding of the benefits and risks of vaccination and the diseases it prevents, enabling them to make evidence-based informed choices and encouraging them to seek immunization services and overcome barriers to vaccination. National vaccination programs should also acknowledge that by developing effective communications plans and capacity, the public's perception of the credibility, trustworthiness, and competence of the program is enhanced.

4.4.3 Optimizing the Provider's Role

Healthcare providers, pediatricians included, remain the most trusted source of information and health advice; however, there is a significant minority of providers in Europe today that do not actively promote vaccination, are vaccine-hesitant, or are outright anti-vaccination. These providers influence their patients and parents. Therefore, national immunization programs need to ensure that the concept of vaccinology and immunology features on medical curricula in medical and nursing colleges and that opportunities for in-service training of healthcare providers are continuously provided and kept up to date. Such education and training should include interpersonal communication techniques and skills to tackle hesitancy.

National vaccination programs should consider reinforcing the learning about vaccine hesitancy and demand determinants with fact sheets and job aids that assist healthcare providers in explaining the risks and benefits of vaccination in a clear and concise way to the parents and patients without the use of jargon or medical terminology. Parents and patients behave more rationally when they receive information in such formats from their credible and trusted healthcare provider. Inconsistent messaging and contradictory information among healthcare providers can confuse patients and parents, prompting mistrust and inaction.

Those healthcare providers that actively advocate and champion vaccination should be identified and supported to share their opinions and engage a broader audience (than the parent/patient and clients they see on a daily basis). These same gatekeepers and influencers also have a role to play in communicating the value and full benefit of vaccines to other providers who themselves are hesitant and those being educated/trained to become healthcare professionals. Professional societies and associations should be considered here as partners in addition to prominent scientists and renowned healthcare luminaries. There is also substantial evidence that vaccine acceptance can be increased by engaging local religious and community leaders, and this should be considered.

4.4.4 Interpersonal Risk Communication

People are hesitant for various reasons, and their levels of concern range from very high to very low. Providers should avoid confrontation and adversarial situations. Rarely do such encounters end with a positive outcome. Providers should adopt an easy-to-understand approach and use frameworks for facing hesitancy, those based on the principles of good risk communication practices. 4-step Framework for Communicating Science: Making the CASE for Vaccines presents such

an approach from the University at Albany's School of Public Health.

- **4-step Framework for Communicating Science: Making the CASE for Vaccines**

Corroborate: – Acknowledge the parents' concern and find some point on which you can agree. Set the tone for a respectful, successful talk.

About me: – Describe what you have done to build your knowledge base and expertise.

Science: – Describe what the science says.

Explain/advise: – Give your advice to the patient, based on the science.

Example: – "I want to spread out the shots so they won't overwhelm my child's immune system."

Corroborate: – Children today certainly have more shots than years ago.

About me: – Our practice follows the national schedule because it is carefully designed to protect children at the time they are most vulnerable to disease. I recently returned from a meeting, or I served on a committee, that reviewed the schedule…

Science: – Although children undergo more shots today, they actually receive fewer antigens than when they had fewer shots, because technology has enabled us to make vaccines that have only the part of the cell that induces immune response. Plus, the immunological challenge from a vaccine is nothing compared with what kids fight off every day. An ear infection is a greater immunological challenge ("Drop in the ocean").

Explain: – We want all the kids in our practice to be immunized so that they have the greatest chance of a long, healthy life. My own children are fully vaccinated.

Providers are advised to communicate the roles and responsibility that the hesitant parent/patient needs to take on if they choose not to vaccinate and to convey that as a health professional he or she is uncomfortable with the parent/patient's decision, emphasizing that it is against the overwhelming scientific consensus. How the healthcare provider introduces immunization at a visit also matters. Taking a presumptive approach, e.g., "Tom is due his vaccinations today," as opposed to a participatory one, e.g., "what do you want to do about vaccinating Tom today?" may also affect the likelihood of immunization acceptance; however, more research is required on this approach. For a very worried hesitant parent/patient, the provider should consider how to find and present extra evidence, information, and narratives and how to dedicate more time, possibly through follow-up appointments. Consider using images and other ways of explaining risks, avoiding jargon and sticking to the facts. At all costs, the provider must maintain the relationship. Parent/patients who are dismissed or feel alienated ultimately find a source, possibly a provider, who supports and agrees with their decision not to vaccinate.

4.4.5 Role of the School

Reaching parents of today and tomorrow by educating pupils (and their parents) in school settings may significantly boost immunization acceptance and resilience of communities. Although little evidence has been generated from vaccination education in school settings, there is evidence that in other areas such as alcohol and substance abuse, sexual and reproductive health, nutrition, and bullying, curricula have shaped beliefs, including the successful development of "Health Promotion schools" under the WHO's Global School Health Initiative. In general, schools provide an important setting for health promotion, with the potential to reach over one billion children worldwide and through them, school staff, families, and whole communities. Providing education on vaccines and immunization in school settings can help children to develop informed critical thinking and decision-making skills, provide knowledge about vaccinations, promote positive attitudes toward immunization, and help to prepare them to make informed choices as parents/patients in the future and be more resilient in the face of anti-vaccine misinformation, including influencing health-related behaviors of the teachers. Pupils around the age of

10 years might be selected as a starting point as they have the cognitive maturity and ability to understand the complexity of the immune system and think beyond the concrete concepts. There are few immunization examples to share, but inclusion of digital learning material, "edutainment," and "gaming," through which teachers and/or parents can guide students to make their own scientific discoveries and witness and understand the history of vaccines, could be adapted from methods used for delivery of other health and social development curricula. Just as education on the environment and ecology has shaped a generation's perception of climate change, so can immunization perceptions be shaped.

4.4.6 Role of the Internet

For active seekers of information, the Internet is an important channel that is growing in terms of its reach and influence on vaccination decisions. In Europe, reliable, trustworthy, easy-to-understand web-based information on vaccine-preventable diseases and the benefits of vaccines is often not available, is difficult to find, or is not in a language that is helpful. Programs have a responsibility to address this and to offer parent/patients and providers a website that is well managed, well resourced, reviewed (format and content), and regularly updated with qualified and well-referenced information. Preferably, these sites should include a mechanism where user feedback and interaction are accommodated – such as a question–answer function. The WHO Global Advisory Committee on Vaccine Safety (GACVS) has compiled a list of websites that provide information on vaccine safety and follow good information practices. GACVS developed four categories of criteria for good information practices – regarding credibility, content, accessibility, and design to which sites providing information on vaccine safety should adhere. Programs are recommended to consider the VSN project when establishing their website and to become a member by meeting the criteria.

4.5 Pain Management

Immunizations are the most commonly recurring health-related procedure undertaken in childhood and the one most associated with needles. For many children, these procedures can cause unnecessary stress and anxiety, which, if not mitigated, can lead to long-term non-adherence with recommended healthcare interventions and missed immunizations. For parents, vaccination sessions can be stressful and involve strong emotional reactions from both the infant/child and the parent. Providers are recommended to familiarize themselves with the WHO position paper *Reducing pain at the time of vaccination (September 2015)* and consider some of the practices proven to reduce pain and anxiety. These include, but are not limited to, techniques to position the child differently or to distract the child. In addition, topical local anesthetic is very effective; however, it was not included in the guideline as it was not readily accessible in low-income countries, but is recommended in Canada's guideline.

4.6 Conclusion

It is evident that the immunization end-user's experiences and perceptions have been undervalued and consequently under-researched. Without understanding these, in addition to the practical and structural barriers to vaccination that people face, immunization programs continue to struggle to equitably extend the benefits of vaccination to protect populations throughout the course of life and across all sectors of society.

There is no strong evidence to recommend any specific intervention for addressing vaccine hesitancy/refusal. Multipronged programs and community- and individual-level strategies, including innovative new methods, should be considered. Interventions should be based upon a degree of audience insight and take into consideration both supply-side modification and parent/patient behavior change, addressing more than a knowledge deficit in addressing hesitancy or sub-optimal demand. Interventions should be tested according to the

target population, the context within which the intervention is to take place, and the degree to which interventions can be tailored. At best, we can be moderately confident in the strategies presented in this chapter, as little research has been conducted into strategies and very few have been evaluated, suggesting that immunization programs might still require focus.

The attention to demand-side factors, themselves at least the counterbalance to supply-side issues, and acknowledgement of the value of behavioral and community insight to direct and inform policy and strategy are necessary developments in Europe. However, it is apparent that immunization program delivery in Europe has some way to go before it becomes people-centric: designed to meet the needs of the end-users and responsive to evolving parent/patient and provider expectations of immunization service delivery.

Further Reading

Butler R, MacDonald NE, SAGE Working Group on Vaccine Hesitancy. Diagnosing the determinants of vaccine hesitancy in specific subgroups: the guide to tailoring immunization programmes (TIP). Vaccine. 2015;33(34):4176–9.

Dubé E, Gagnon D, MacDonald NE, SAGE Working Group on Vaccine Hesitancy. Strategies intended to address vaccine hesitancy: review of published reviews. Vaccine. 2015;33(34):4191–203.

European Centre for Disease Prevention and Control. Countering online vaccine misinformation in the EU/EEA. Stockholm: ECDC; 2021. Stockholm, June 2021 ISBN: 978-92-9498-542-2 https://doi.org/10.2900/329304 Catalogue number: TQ-09-21-276-EN-N https://www.ecdc.europa.eu/en/publications-data/countering-online-vaccine-misinformation-eu-eea.

Fu LY, Zook K, Gingold JA, Gillespie CW, Briccetti C, Cora-Bramble D, Joseph JG, Haimowitz R, Moon RY. Strategies for improving vaccine delivery: a cluster-randomized trial. Pediatrics. 2016;137(6). pii: e20154603.

Gesser-Edelsburg A, Walter N, Shir-Raz Y, Sassoni Bar-Lev O, Rosenblat S. The behind-the-scenes activity of parental decision-making discourse regarding childhood vaccination. Am J Infect Control. 2016. pii: S0196-6553(16)30962-2. https://doi.org/10.1016/j.ajic.2016.10.009.

Goldstein S, MacDonald NE, Guirguis S, SAGE Working Group on Vaccine. Health communication and vaccine hesitancy. Vaccine. 2015;33(34):4212–4.

Harvey H, Reissland N, Mason J. Parental reminder, recall and educational interventions to improve early childhood immunisation uptake: a systematic review and meta-analysis. Vaccine. 2015;33(25):2862–80.

Jarrett C, Wilson R, O'Leary M, Eckersberger E, Larson HJ, SAGE Working Group on Vaccine. Hesitancy strategies for addressing vaccine hesitancy - a systematic review. Vaccine. 2015;33(34):4180–90.

Larson HJ, Smith DM, Paterson P, Cumming M, Eckersberger E, Freifeld CC, et al. Measuring vaccine confidence: analysis of data obtained by a media surveillance system used to analyse public concerns about vaccines. Lancet Infect Dis. 2013;13(7):606–13.

Leask J, Kinnersley P, Jackson C, Cheater F, Bedford H, Rowles G. Communicating with parents about vaccination: a framework for health professionals. BMC Pediatr. 2012;12:154.

MacDonald NE, SAGE Working Group on Vaccine Hesitancy. Vaccine hesitancy: definition, scope and determinants. Vaccine. 2015;33(34):4161–4.

MacDonald NE, Finlay JC, Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Working with vaccine-hesitant parents. Paediatr Child Health. 2013;18(5):265–7.

MacDonald NE, Butler R, Dubé E. Addressing barriers to vaccine acceptance: an overview. Hum Vaccin Immunother. 2018;14(1):218–24. Received 10 Oct 2017, https://doi.org/10.1080/21645515.2017.1394533.

Ndeffo Mbah ML, Liu J, Bauch CT, Tekel YI, Medlock J, Meyers LA, Galvani AP. The impact of imitation on vaccination behavior in social contact networks. 2012. https://doi.org/10.1371/journal.pcbi.1002469.

Nowak GJ, Gellin BG, MacDonald NE, Butler R, SAGE Working Group on Vaccine Hesitancy. Addressing vaccine hesitancy: the potential value of commercial and social marketing principles and practices. Vaccine. 2015;33(34):4204–11.

Nyhan B, Reifler J, Richey S, Freed GL. Effective messages in vaccine promotion: a randomized trial. Pediatrics. 2014;133(4):e835–42.

Odone A, Ferrari A, Spagnoli F, Visciarelli S, Shefer A, Pasquarella C, Signorelli C. Effectiveness of interventions that apply new media to improve vaccine uptake and vaccine coverage. Hum Vaccin Immunother. 2015;11(1):72–82.

Report for the European Commission. de Figueiredo A, Karafillakis E and Larson HJ. State of Vaccine Confidence in the EU and UK. 2020. https://ec.europa.eu/health/vaccination/confidence_en.

Schmidt P, MacDonald NE, Habersaat K, Butler R. Commentary to: how to respond to vocal vaccine deniers in public. Vaccine. 2016. pii: S0264-410X(16)30914-8 ahead of print.

Shelby A, Ernst K. Story and science: how providers and parents can utilize storytelling to combat anti-vaccine misinformation. Hum Vaccin Immunother. 2013;9(8):1795–801.

World Health Organization Regional Office for Europe. 2012. Information for parents. If you choose not to vaccinate your child, understand the risks and

responsibilities. http://www.euro.who.int/__data/assets/pdf_file/0004/160753/If-You-Choose-Not-to-Vaccinate.pdf?ua=1.

World Health Organization. Report of the SAGE Working Group on Vaccine Hesitancy. http://www.who.int/immunization/sage/meetings/2014/october/SAGE_working_group_revised_report_vaccine_hesitancy.pdf?ua=1.

World Health Organization. Reducing pain at the time of vaccination: WHO position paper – September 2015. Wkly Epidemiol Rec. 2015;90:505–10.

World Health Organization European Region. How to respond to vocal vaccine deniers in public. 2017. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/viewer.html?pdfurl=https%3A%2F%2Fwww.euro.who.int%2F__data%2Fassets%2Fpdf_file%2F0005%2F315761%2FVocal-vaccine-deniers-guidance-document.pdf.

World Health Organization European Region. Vaccination and trust: how concerns arise and the role of communication in mitigating crises. 2017. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/viewer.html?pdfurl=https%3A%2F%2Fwww.euro.who.int%2F__data%2Fassets%2Fpdf_file%2F0004%2F329647%2FVaccines-and-trust.PDF.

Adjuvants in Pediatric Vaccines

Nathalie Garçon

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_5

5.1 Introduction

The exponential evolution of scientific knowledge during the first half of the twentieth century led to the emergence of new and improved ways of producing vaccines. Vaccines were produced from cultivating the pathogens, but this has not always been possible in sufficient quantities. The rise of molecular biology and a better understanding of the key components of immune protection have allowed the development and production of what is known as recombinant antigens. Most, if not all purified and recombinant antigens, require to be effective the addition of what is known today as adjuvants. They are an important part of the development of improved or new vaccines against infectious diseases, alongside DNA or vector-based vaccines, and may be required with oligonucleotide-based vaccines if not self adjuvanted.

5.2 Definition of Adjuvants

An adjuvant, from the Latin word adjuvare meaning to help or aid, is a substance used to improve a vaccine's immune response by accelerating, prolonging, or enhancing the immune responses specific to the vaccine antigen(s), in particular by increasing mean antibody (Ab) titers of the population being immunized.

It is clearly accepted today that all current whole, attenuated, subunit, purified recombinant protein and peptide vaccines are adjuvanted endogenously (part of the pathogen) or exogenously (added to the antigen formulation).

Indeed, during this evolution moving from whole killed or attenuated pathogens to particulate vaccines, combined with the tools of modern biotechnology, vaccines have not only seen an increased safety and lowered reactogenicity profile but also the loss of many of immunological stimuli needed to trigger an effective immune response. For these vaccines, adjuvants became an important tool to ensure efficient and lasting immune response.

Until the early 1980s, adjuvantation science was limited to the use of aluminum salts. Following the emergence of HIV and the following attempts to develop HIV vaccines, it appeared that aluminum salts were not enough to induce a protective immune response when combined with recombinant antigens. This revived the interest in adjuvants, and over the past 30 years, there has been an exponential growth of information regarding pattern recognition receptors (PRRs) that can activate leukocytes and thereby enhance immune responses.

When properly designed, selected, and combined with the relevant antigen(s), adjuvants can enable the appropriate and long-lasting immune response required to protect against the disease, with a safety profile acceptable in the targeted population. To date, no combination of recombinant antigen and adjuvant has demonstrated the ability to induce a CD8 immune response in naive human subjects, and adjuvants that enhance CD4 T cell responses are critical for durable vaccine immunity.

The understanding of the mode of action of adjuvants has greatly benefited from the discovery of pathogen-associated molecular patterns (PAMPs) and their associated receptors (Toll-like receptors [TLRs], nucleotide-binding oligomerization domain [NOD]-like receptors [NLR]) and inflammasome components and has been critical to the understanding of the link between innate and adaptive immunity and the associated pivotal role of dendritic cells. Despite these advances, a rational design approach would clearly benefit from a better understanding of the roles of innate and adaptive immunity and their impact on vaccine safety and immunogenicity.

5.3 Adjuvants in Vaccines

New vaccines based on recombinant antigens and adjuvants have put vaccine formulation at the center of vaccine development. Chemical structure, physicochemical characteristics, stability, the nature of the induced immune response, the impact on innate immune response, and the mode of action are key for their evaluation and use.

Table 5.1 Adjuvants in vaccines licensed for pediatric populations

Aluminum salts	Phosphate or hydroxide	D, T, Pa, Hib, HBV, HAV, IPV, pneumococcus, HPV
Emulsion	MF59	Seasonal influenza
	AS03	Pandemic influenza H1N1 and H5N1
	AF03	Pandemic influenza H1N1
Liposomes	Virosomes	Seasonal influenza
Combination	Aluminum + MPL	HPV

To date, there are nine different adjuvants present in licensed adjuvanted vaccines. Amongst those, seven are licensed for use in pediatric populations (Table 5.1).

5.4 Aluminum Salts

The evaluation and use of aluminum salts in vaccines emerged in 1921 when a diphtheria vaccine based on inactivated diphtheria toxin (toxoid) was shown to be protective against diphtheria toxin. In 1926, aluminum precipitation was shown to enhance antibody response to diphtheria toxoid in guinea pigs, and in 1932 it was shown that alum enhances response to diphtheria toxoid immunization in humans. In 1939, Al-hydrogel became commercially available, and since then, several billions of aluminum-containing vaccine doses have been used around the world. Several types of aluminum salts have been developed. They are particulate in nature and are different with regard to their surface charge, allowing effective adsorption of the antigen depending on its point of zero charge (pH at which the antigen has a neutral charge). The antigen adsorption increases the specific immune response and the antigen stability. Aluminum adjuvants are present in most of the currently licensed vaccines (Table 5.2). Although aluminum-containing vaccines are licensed across the world, the amount of Al present in a vaccine can vary depending on the country considered (Table 5.3).

Table 5.2 Aluminum-containing vaccines licensed for pediatric vaccines

Adjuvant	Vaccine
Alum: aluminum potassium sulfate Alhydrogel: aluminum hydroxide Adju Phos: aluminum phosphate Proprietary aluminum hydroxide and phosphate	DTaP (pediatric diphtheria, tetanus and acellular pertussis)
	DTaP, polio and *Haemophilus influenzae* type b
	DTaP, polio, *Haemophilus influenzae* type b and hepatitis B
	Hepatitis A
	Hepatitis B
	Hepatitis A/B
	Human papillomavirus-6/11/16/18
	Influenza (H5N1)
	Pneumococcus (conjugated)
This is not an exhaustive list; it focuses on the USA and Europe	

The mode and mechanism of action by which aluminum salts have an impact on the human immune system are not fully deciphered and appear to be both direct and indirect. Through the transformation of antigens into a particulate through their adsorption on aluminum salts, antigen interaction with antigen-presenting cells (APCs) and macrophages is optimized compared to a soluble antigen formulation. To date, various possible mechanisms of action have been described (Table 5.4).

Aluminum salts have the longest and largest safety track record of all adjuvanted vaccines, with more than three billion vaccine doses used during the past 80 years and a positive risk–benefit ratio. Focal histological lesions were observed in vaccinees with diffuse muscular symptoms that included persistent myalgias, arthralgias, and persistent fatigue. In

Table 5.3 Limits of elemental aluminum (Al^{3+}), reported per human dose

Region	Reference/product	Limit (Al^{3+}) mg/dose
USA	21CFR Part 610 "General Biological Products Standards"	0.85
EU	European pharmacopoeia "Vaccines for Human Use"	1.25
WHO	WHO technical report series	1.25
China	DTPa	0.17–0.26
	Diphtheria vaccine adsorbed	0.52
	Tetanus vaccine adsorbed	0.52
	Diphtheria and tetanus combined vaccine, adsorbed	0.43
	HAV	0.60
	HBV	0.18–0.31
Japan	Adsorbed purified pertussis	0.15
	Adsorbed diphtheria-purified pertussis-tetanus	0.15
	HPV	0.42–0.58
	Recombinant adsorbed hepatitis B vaccine	0.325
India	HBV	1.25
	DTP	1.25

Table 5.4 Mode of action of aluminum

Crystalline alum binds lipids on the surface of DCs	Cellular activation cascade triggering an immune response
Directly or indirectly triggers innate immunity through activation of inflammasome complexes	Likely nucleotide-binding oligomerization (NOD)-like receptor (NLR)-mediated effect is still present in MyD88 and TRIF in knockout mice
Induces cell death, which modulates the environment towards an enhanced adaptive immune response	Damage-associated molecular pattern release, such as uric acid and dsDNA, act as autologously derived autoadjuvants

the approximately 130 cases observed, these lesions were identified as macrophagic myofasciitis (MMF). Intracytoplasmic inclusions in the infiltrating macrophages have been identified as containing aluminum by electron microscopy, microanalysis, and atomic adsorption spectroscopy. There is no established relationship between the presence of aluminum and MMF and the clinical symptoms, however. The Vaccine Safety Advisory Committee of the World Health Organization (WHO) reviewed MMF during a meeting in 1999 and found no basis for recommending a change in vaccination practices (vaccine selection, schedule, delivery practices, or information on aluminum-containing vaccines). Studies have been undertaken since then, to evaluate the clinical, epidemiological, and basic science aspects of MMF. Although it is recognized that aluminum salts may be found months or years later at the intramuscular injection site after vaccination, to date, no link has been clearly established with the MMF syndrome.

5.5 Emulsions

Since the development of Freund's adjuvant, numerous emulsions have been evaluated in human. Water-in-oil emulsions (emulsified water droplets in a continuous oil phase) have been removed from testing following unacceptable reactogenicity (cysts at the injection site) and a lack of formulation reproducibility. The development of alternative emulsions (oil-in-water where oil droplets are in a continuous aqueous phase) was then undertaken. They represent the class of emulsion currently licensed in pediatric vaccines. They are made of particles of less than 200 μm (allowing for sterile filtration), are made of metabolizable naturally occurring oils such as squalene, and are stabilized by nonionic surfactants such as Tween 80 and Span 85. They have been shown

to enhance antibody responses and allow for antigen dose sparing particularly seasonal and pandemic influenza vaccines, using MF59 (Fluad, Focetria), AS03 (Pandemrix), and AF03 (Humenza) as adjuvants. Oil-in-water emulsion can have a deleterious effect on antigen stability depending on the nature of the antigen and has not yet been shown to improve antigen stability. Their mechanism of action may vary depending on the emulsion considered. Post H1N1pdm09 vaccination, reports of narcolepsy caused great concern. Narcolepsy was observed following the use of ASO3 adjuvanted H1N1sw vaccine in several European countries, including Sweden, Finland, and the UK. The current hypothesis points towards a role of a CD4 T cell mimicry sequence in the nucleoprotein and neuraminidase proteins of A/H1N1pdm09. The role of ASO3 adjuvant cannot be excluded. The H1N1pdm09 vaccine is recommended for individuals above 20 years of age by EMA, but is not in use anymore (see ► Chap. 14).

5.6 Virosomes

Virosomes are liposome-based formulations that can incorporate hydrophobic components within their membrane and hydrophilic ones as a cargo within the particle internal volume. They can act both as antigen carrier and adjuvant through the incorporation of immunomodulatory molecules.

In the case of Inflexal (seasonal influenza vaccine), the virosomes are made up of empty influenza virus envelopes that present the HA antigen within their membranes.

The mode of action of virosomes is not yet understood. It is, however, hypothesized that it relies on binding to macrophages and APC membranes, leading to the engagement of the innate and adaptive immune mechanisms.

5.7 TLR4 Agonists and Adjuvant Systems

At the forefront of PRRs are detoxified congeners of endotoxin that stimulate TLR4. Present in Cervarix, one of the human papilloma virus vaccines, it is derived from lipopolysaccharide, the *Salmonella minnesota* lipopolysaccharide, through a specific process that allows for a very significant reduction of its pyrogenicity (2–3 log) while retaining its adjuvant effect. In this vaccine, monophosphoryl lipid A (MPL) is combined with aluminum hydroxide and is known as AS04 adjuvant. Its mode and mechanism of action have been thoroughly evaluated. The efficacy and safety report in the target population has allowed for vaccine registration worldwide, making AS04 the first adjuvant, other than aluminum salts, to be present in a licensed vaccine in the USA.

5.8 Additional Adjuvants in Development

Building on the successful results obtained with MPL, and a better understanding of the mechanisms of action of the current immunomodulators, a number of additional adjuvants are being evaluated in the context of various vaccines.

5.8.1 Defined Agonists of PRRs

Numerous PRR agonists targeting TLRs, NOD-like receptors, or retinoic acid-inducible gene (RIG)-like receptors have been evaluated in adult human clinical trials. Several TLR agonists such as double-stranded ribonucleic acid (dsRNA), flagellin, single-stranded RNA, or CpG have demonstrated different levels of activity. Several have also been shown to be capable of inducing an effective immune response in animal models, including mucosal adjuvants. Those capable of targeting the endosomal compartment have demonstrated the most robust impact on cellular immunity so far.

5.8.2 Saponins

As most of the adjuvants used or developed for human vaccines have shown strong local

reactogenicity, efforts have been undertaken to purify out from the mixture a specific molecule (QS21) that presents the optimum ratio between adjuvant effect and low local reactogenicity. This, however, was not sufficient to fully abrogate the lytic activity observed, and improvement through formulation was developed. The ability of Quil-A saponins to interact strongly with cholesterol was the cornerstone of the two formulations that were developed: one, known as ISCOMs/ISCOMATRIX, uses specific fractions of Quil-A; the other uses specific cholesterol-containing liposomes that are able to completely quench the lytic activity while retaining the adjuvant activity. This later adjuvant combined with MPL is known as AS01 and is present in the malaria candidate vaccine RTS,S, as well as the recombinant zoster vaccine. AS01 acts through the TLR4 activation capability of MPL and increases APC recruitment and activation, leading to a stronger and more persistent immune response.

5.8.3 Particulates

The use of particulates in vaccines goes back to the early 1920s when G. Ramon, then at the Pasteur institute, developed a method of increasing the production of hyperimmune sera while avoiding the frequent abscesses observed in horses after toxoid administration. It is the adsorption of antigens on those particles that increases the immune response (the principle used for aluminum salts) and decreases or prevents abscesses by the concomitant adsorption of endotoxins. Biodegradable polymers (such as polylactic, polyglycolic) have been extensively explored with the hope of designing nano- or microparticles, where the antigens could be entrapped within or adsorbed on their surface. This should allow for a slow release of the antigens, leading to a single-shoot vaccine approach. Those polymers, however, due to their sensitivity to hydrolysis, need to be lyophilized and kept in a humidity-controlled environment until use.

Recent advances in polymer synthesis and particle engineering have allowed for the development of delivery systems with defined size, shape, and components, allowing for an approach tailored to the antigen to be delivered and cell or cell compartment to be targeted. This has the potential for a rational design approach to the field of vaccine delivery systems.

5.9 Specific Needs for the Pediatric Population

Today, pediatric populations are the primary beneficiary of vaccination, whereas most adjuvant research and development is done for vaccines to be used in older populations. As many of the adjuvants described above can have a varying impact on immunogenicity and reactogenicity when applied to younger populations, a better understanding of the immune status and its evolution across ages, in addition to the impact of adjuvants in those settings, is critical to understand how adjuvants may be best used in children.

5.9.1 Immunogenicity

The emergence and development of new tools first applied to drug discovery such as medicinal chemistry for the design and synthesis of molecules tailored to the need for early life immunity, their evaluation in high-throughput models based on infants' leukocytes, and their optimization through modern computational algorithms can reasonably be seen as the next step toward the rational design of adjuvants for all target populations, including pediatrics.

The evaluation of a vaccine's immunogenicity and efficacy in animal models predictive of infant human populations can be expensive and unpredictable. In vitro approaches, which have the potential to accurately reflect the in vivo activity of those adjuvants in the target population, would allow for a rational design and selection of the adjuvant to be used and a focused preclinical evaluation. Given the leaps that are being made today, both in fundamental science and in technology development such as organ on a chip, these approaches may be a reality in the near future.

5.9.2 Reactogenicity

A key concern regarding adjuvanted vaccine development is reactogenicity, i.e., the ability of a formulation to cause acute inflammatory events locally or systemically (such as fever). Their optimization may require adaptations such as modifying their pharmacokinetic properties to affect their biodistribution or tailoring the formulation to ensure co-delivery of the antigen(s) and adjuvant to the same APC. The discovery of biomarkers as surrogate markers of in vivo reactogenicity would allow for the rational screening of potential candidates and accelerate the selection of the optimal candidate for a specific vaccine.

Vaccines and Adjuvants

The emergence of SARS-CoV-2, its speed of spread, and case fatality in specific populations have prompted a fast track development of candidate vaccines. To date tens of vaccines are in clinical trials, based on classical technology platforms (recombinant antigens and adjuvant, attenuated or killed pathogens vaccines) or more pioneering ones such as mRNA and live vectors. Three vaccines are being developed based on the spike protein S adjuvanted with AS03, CpG or matrix adjuvant. Matrix adjuvant is a saponin lipid particle-based adjuvant which is combined to a subunit S protein in Novavax NVX-CoV2373 vaccine. It has demonstrated an 89.3% efficacy against the primary and England strains and a protection of 60% against the South African variant. Two other recombinant antigen vaccines based on S protein (Sanofi Pasteur and Medicago) are using AS03 (or matrix for Medicago). Both vaccines are in PIII clinical trials. It will be of value to see if when using AS03 adjuvant the immune response induced will allow for a broader protection against the emerging variants.

To date, mRNA vaccines have demonstrated their ability to be produced and delivered faster than any current platforms. Long-lasting protection as well as reactogenicity profile is still to be established, and one cannot exclude that addition of adjuvant will be needed.

5.10 Conclusion

The emergence of new diseases that can affect populations of all ages worldwide, in addition to the re-emergence of childhood diseases, needs to be tackled using new or improved technologies. Adjuvants have been, for the past decades, one of the most promising advances in the development of new or improved vaccines. They have been developed and tested to a large extent for and in the adult population. Little has been done to specifically design adjuvants that are best suited to pediatric populations, in part because of the less advanced understanding of the pediatric immune system and the challenges posed by the small size of infants.

Given the evolution of knowledge and technologies observed during the last few decades, it is possible today to envision the identification of biomarkers predictive of better safety and immunogenicity that allow for their targeted use in pediatric populations when and where needed.

Further Reading

Awate S, et al. Mechanisms of action of adjuvants. Front Immunol. 2013;4:114.

Bachmann MF, Jennings GT. Vaccine delivery: a matter of size, geometry, kinetics and molecular patterns. Nat Rev Immunol. 2010;10:787–96.

Brenner A. Macrophagic myofasciitis: a summary of Dr. Gherardi's presentations. Vaccine. 2002;20(Suppl 3):S5–6.

Broadbenta A, Subbaraoa K. Influenza virus vaccines: lessons from the 2009 H1N1 pandemic. Curr Opin Virol. 2011;1(4):254–62.

Didierlaurent A, et al. Adjuvant system AS01: helping to overcome the challenges of modern vaccines. Expert Rev Vaccines. 2017;16:55–63.

EMA. Assessment report immunological differences of pandemic vaccines (review of hypothesis on Pandemrix and development of narcolepsy). 2012. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000832/WC500118056.pdf.

Garçon N. Development of an AS04-adjuvanted HPV vaccine with the adjuvant system approach. Biodrugs. 2011;25(4):217–26.
Garcon N, Friede M Evolution of Adjuvants Across the Centuries, Plotkins Vaccine, 7th edition 2018, Pages 61–74.
Glenny AT, Sudmersen HJ. Notes on the production of immunity to diphtheria toxin. J Hyg. 1921;20:176.
Gomes AC, Mohsen M, Bachmann MF. Harnessing nanoparticles for immunomodulation and vaccines. Vaccines (Basel). 2017;5.
Latorre D, Kallweit U, Armentani E, Foglierini M, Mele F, Cassotta A, et al. Tcells in patients with narcolepsy target self-antigens of hypocretin neurons. Nature 2018;562:63–8.
Luo G, Ambati A, Lin L, Bonvalet M, Partinen M, Ji X, et al. Autoimmunity to hypocretin and molecular mimicry to flu in type 1 narcolepsy. Proc Natl Acad Sci USA 2018;115:E12323–32.
Park WH, Schroder MC. Diphtheria toxin-antitoxin and toxoid: a comparison. Am J Public Health Nations Health. 1932;22:7–16.
Plotkin SA, Plotkin SL. The development of vaccines: how the past led to the future. Nat Rev Microbiol. 2011;9:889–93.
PrabhuDas M, et al. Challenges in infant immunity: implications for responses to infection and vaccines. Nat Immunol. 2011;12(3):189–94.
Riedel S. Edward Jenner and the history of smallpox and vaccination. Proc (Bayl Univ Med Cent). 2005;18(1):21–5.
Rowley DA, Fitch FW. The road to the discovery of dendritic cells, a tribute to Ralph Steinman. Cell Immunol. 2012;273(2):95–8.
Schwendener R. Liposomes as vaccine delivery systems: a review of the recent advances. Ther Adv Vaccines. 2014;2(6):159–82.
Vaarala O, Vuorela A, Partinen M, Baumann M, Freitag TL, Meri S, et al. Antigenic Differences between AS03 Adjuvanted Influenza A (H1N1) Pandemic Vaccines: Implications for Pandemrix-Associated Narcolepsy Risk. PLoS One. 2014;9(12):[114361]. https://doi.org/10.1371/journal.pone.0114361.
Vuorela A, Freitag TL, Leskinen K, Pessa H, Härkönen T, et al. Enhanced influenza A H1N1 T cell epitope recognition and cross-reactivity to protein-O-mannosyltransferase 1 in Pandemrix-associated narcolepsy type 1. Nature Communications. 2021;12(1):[2283]. https://doi.org/10.1038/s41467-021-22637-8.

Maternal Immunization

Timo Vesikari, Kirsten Maertens, and Adam Finn

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_6

6.1 Live Viral Vaccines

In general, the use of live-attenuated vaccines is contraindicated or not recommended during pregnancy based on a theoretical risk of transmission of the virus through the placenta resulting in an infection of the fetus.

Live attenuated rubella vaccine virus can cross the placenta but is not known to cause congenital rubella nor, in fact, any symptoms in the fetus or newborn. Nevertheless, rubella vaccine is contraindicated in pregnancy. Single rubella vaccine is no longer available, but the same applies for MMR (measles-mumps-rubella) vaccine although the measles and mumps components are not known to pass transplacentally. If MMR vaccine is indicated for women of childbearing age, pregnancy should be excluded before vaccine administration, and contraceptive precautions should be advised for 1 month following vaccination.

However, if MMR vaccine is given inadvertently, no specific measures need to be taken. The vast clinical experience of inadvertent administration of rubella and MMR vaccination suggests that these vaccines will not cause any harm to the fetus.

Live attenuated varicella and MMRV vaccines should be treated like MMR, i.e., not given in pregnancy but, if given accidentally, no specific measures taken.

Live intranasal influenza vaccine should not be given in pregnancy, while non-live vaccine is widely recommended.

6.2 Tetanus Immunization

Maternal and neonatal tetanus is an important cause of maternal and neonatal morbidity and mortality. Neonatal tetanus was estimated to be responsible for 787,000 deaths globally in the early 1980s. Therefore, the WHO (World Health Organization) launched the Maternal and Neonatal Tetanus Elimination program in 1989.

WHO recommends that unimmunized pregnant women or pregnant women without documentation of previous tetanus vaccination should receive two doses of tetanus toxoid at least 4 weeks apart. The first dose should be given as early as possible during pregnancy, and the last dose should be given at least 2 weeks prior to delivery.

The program has been a great success: in 2001, it was estimated that the mortality had fallen to 180,000 deaths annually and in 2018 to only 25,000.

The vast experience accumulated in the global effort to eliminate neonatal tetanus by vaccination during pregnancy provides valuable evidence of general safety of non-live vaccines in pregnant women and in this way has been part of the foundation for current immunizations in pregnant women with Tdap vaccines in Europe and elsewhere.

6.3 Pertussis Immunization

Infant immunization program in Europe starts at 2 or 3 months of age, and protection is insufficient after one dose. Thus, infants remain susceptible to pertussis for several months at the age when pertussis is most dangerous. With the introduction of acellular pertussis vaccines, the immunity level in young people surrounding the newborn, and indeed in young mothers, will be lower than before and the risk to newborn infants of severe pertussis even greater.

In the UK, a resurgence of pertussis in newborns with an increase of deaths was observed in 2012, and the authorities responded quickly by offering vaccine to pregnant women. The program has been highly successful and had reached around 80% coverage. The program has successfully prevented pertussis deaths in neonates, and the only two reported pertussis deaths where vaccine was used were in infants of mothers immunized only shortly before delivery (Fig. 6.1).

Immunizing pregnant women with a tetanus, diphtheria, and acellular pertussis (aP) (Tdap) vaccine results in an increase in pertussis-specific antibodies in the pregnant women. Since these pertussis-specific antibodies wane quite rapidly, Tdap immunization is recommended in every pregnancy to augment the transport of antibodies across the pla-

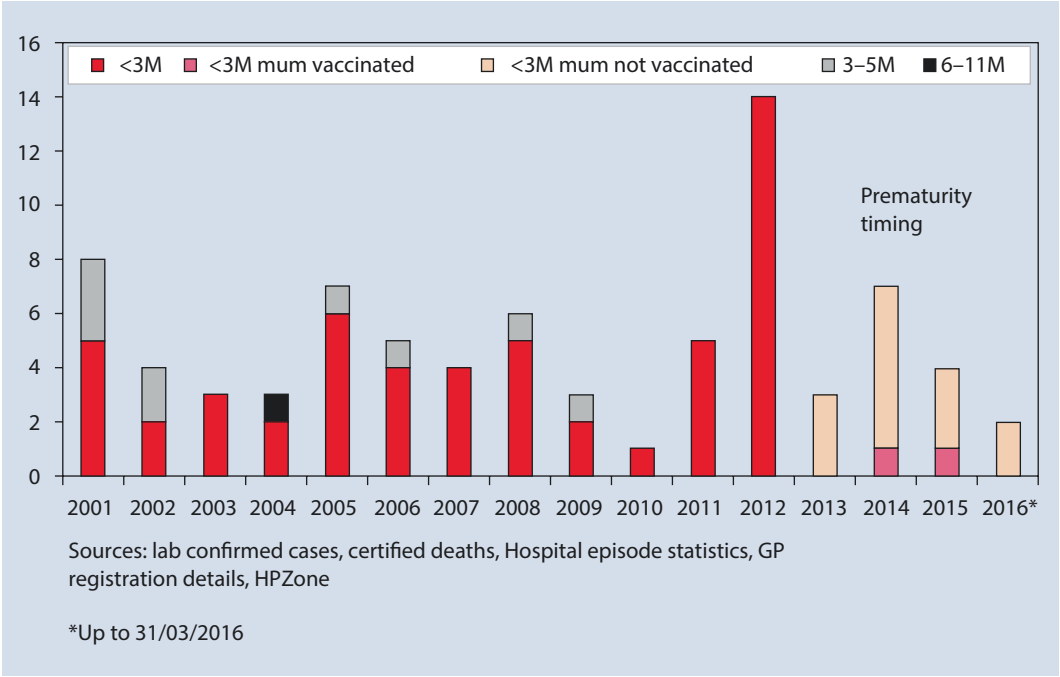


Fig. 6.1 Reconciled deaths from pertussis in infants, England 2001–2015. (From: ▶ https://www.gov.uk/government/publications/vaccination-against-pertussis-whooping-cough-for-pregnant-women. Vaccination against pertussis (whooping cough) for pregnant women: an update for healthcare professionals)

centa towards the fetus and to maximize passive neonatal immunity.

The presence of high levels of maternal antibodies induced by vaccination during pregnancy is associated with a modulation of the infant immune responses to childhood vaccination, a phenomenon called interference or blunting. Administration of Tdap during pregnancy results in a modulation of the infant immune response to their own routine childhood immunization, including pertussis, diphtheria, tetanus, and antibody responses to pneumococcal vaccines. Recent studies have shown that this modulation of the infant immune response did not result in a reduction of the percentage of children with seroprotective antibody levels, nor in an increase of the incidence of infectious diseases later in life. Therefore, clinical consequences of this modulation are highly unlikely.

While the UK program aims to prevent infant pertussis, in practice a Tdap-polio combination vaccine, such as Boostrix-IPV, is given to pregnant women. Other countries, notably Belgium in 2013, have followed the UK model and started vaccination of pregnant women with combination vaccine. However, Europe is divided in this regard, and the majority of countries do not (yet) recommend pertussis vaccination of pregnant women.

In the USA, a CDC-conducted case-control study showed that Tdap vaccination in the third trimester of pregnancy has a vaccine efficacy of 90.5% (CI 65.2–97.4%) for prevention of pertussis-associated hospitalizations in the newborn. This has led to a CDC recommendation that all mothers get a Tdap vaccination between 27 and 36 weeks of each pregnancy.

6.4 Influenza Vaccination

With the emergence of H1N1pdm09 pandemic, it was soon recognized that swine flu was serious and more often fatal in pregnant women. When monovalent H1N1pdm09 vaccines became available in late 2009, they were recommended and given to pregnant women

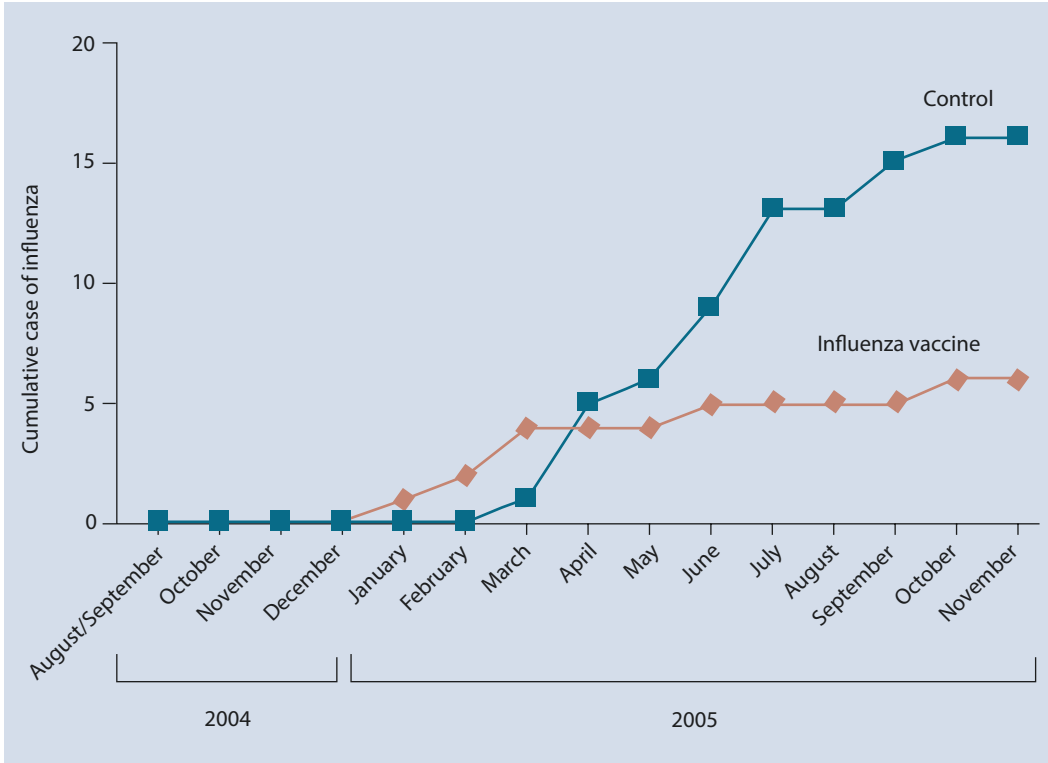


Fig. 6.2 Prevention of influenza up to 6 months of age in infants whose mothers received influenza vaccine during pregnancy. (From: Zaman et al. (2008))

to protect them against severe pandemic influenza. Several studies were conducted on safety and efficacy of this practice, and it was confirmed that the vaccine protected pregnant women and was not only safe for the fetus but actually decreased fetal complications.

Meanwhile, in 1998, Neuzil and coworkers had already shown that influenza vaccination reduces the risk of severe complications of seasonal influenza in pregnancy. This had already led to consideration of influenza vaccination of pregnant women, and the good experience of H1N1pdm09 vaccination formed another stimulus for the US ACIP in 2010 to reinforce recommendations for influenza vaccination for all women who are pregnant during influenza season. In 2012 WHO stated that influenza vaccination of pregnant women is a "highest priority." Several European countries have adapted the recommendation, and others may follow as there is no clear opposition to this recommendation in contrast to pertussis vaccine.

Influenza vaccine can be given during any trimester of pregnancy. Influenza vaccination reduces the risk of prematurity and the risk of low birth weight.

Influenza vaccination for pregnant women has also been documented to protect infants against influenza up to 6 months of age (Fig. 6.2). This is of particular importance, because young infants are a high-risk group for influenza deaths and there is no influenza vaccination policy in sight for direct protection of infants younger than 6 months of age.

6.5 Future Prospects

Maternal immunization is one option under investigation for prevention of severe respiratory syncytial virus (RSV)-associated disease

in the infant. A proof-of-principle efficacy trial was recently published and gives an idea of the effectiveness of this approach.

The vaccine that has reached phase 3 trial is RSV fusion (F) protein nanoparticle vaccine produced in insect cells (Novavax). The vaccine contains the epitope that is the target of palivizumab monoclonal antibody and other epitopes. In the trial about 4500 pregnant women were vaccinated between 28 and 36 weeks of gestation, and infants were followed for RSV disease for 90 days and up to 180 days. In the 90-day follow-up, 3.7% infants in the placebo group and 2.1% in the vaccine group were hospitalized for RSV-associated lower respiratory tract disease (VE 44.4%, 95% CI 19.6–61.5%).

It remains to be seen if this level of protection will be sufficient for licensure. Secondly maternal immunization will be compared to prevention of RSV disease in the infant by new immunoglobulins.

Other vaccines are in development with a potential to be given during pregnancy to prevent severe neonatal bacterial infections including group B streptococcal vaccine (see related chapters in Part IV).

Further Reading

Maternal Immunization in General

Abu Raya B, Maertens K, Edwards K, et al. Global Perspectives on Immunization During Pregnancy and Priorities for Future Research and Development: An International Consensus Statement. Front Immunol. 2020;11:1282.

Maertens K, Orije MRP, Van Damme P, Leuridan E. Vaccination during pregnancy: current and possible future recommendations. Eur J Pediatr 2020;179(2):235−242.

Marchant A, Sadaranghani M, Garand M, Dauby N et al. Maternal immunization: collaborating with mother nature. Lancet Infect Dis 2017;17:e197−208.

Tetanus

Demicheli V, Barale A, Rivetti A. Vaccines for women for preventing neonatal tetanus. Cochrane Database Syst Rev. 2015;(7):CD002959.

Pertussis

Amirthalingham G, Campbell H, Ribeiro S, Fry NK et al. Sustained effectiveness of the maternal pertussis immunization program in England 3 years following the introduction. Clin Infect Dis 2016;63 (suppl 4): S236−S243.

Maertens K, Caboré RN, Huygen K, Vermeiren S, Hens N, Van Damme P, Leuridan E. Pertussis vaccination during pregnancy in Belgium: follow-up of infants until 1 month after the fourth infant pertussis vaccination at 15 months of age. Vaccine. 2016;34(31):3613–9.

Maertens K, Burbidge P, Van Damme P, Goldblatt D, Leuridan E. Pneumococcal immune response in infants whose mothers received Tdap vaccination during pregnancy. Pediatr Infect Dis J. 2017;36(12): 1186−1192.

Munoz FM, Bond NH, Maccato M, Pinell P, Hammill HA, Swamy GK, et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. JAMA. 2014;311:1760–9.

Wanlapakorn N, Maertens K, Vongpunsawad S, Peunpa J, Tran TMP et al. Quantity and quality of antibodies after acellular versus whole cell pertussis vaccines in infants born to mothers who received Tdap during pregnancy: a randomized trial. Clin Infect Dis 2020;71(1):72−80.

Influenza

Abu Raya B, Edwards KM, Scheifele DW, Halperin SA. Pertussis and influenza immunization during pregnancy: a landscape review. Lancet Infect Dis 2017;17:e209−22.

Fell DB, Platt RW, Lanes A, et al. Fetal death and preterm birth associated with maternal influenza vaccination: systematic review. BJOG. 2015;122:17–26.

Håberg SE, Trogstad L, Gunnes N, et al. Risk of fetal death after pandemic influenza virus infection or vaccination. N Engl J Med. 2013;368:333–40.

McMillan M, Porritt K, Kralik D, Costi L et al. Influenza vaccination during pregnancy: a systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes. Vaccine 2015;33:2108−2117.

Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol. 1998;148:1094–102.

Sakala IG, Honda-Okubo Y, Fung J, Petrovsky N. Influenza immunization during pregnancy: benefits for mother and infant. Hum Vaccin Immunother. 2016;12(12):3065–71.

Savulescu C, Jiménez-Jorge S, de Mateo S, et al. Using surveillance data to estimate pandemic vaccine

effectiveness against laboratory confirmed influenza A(H1N1)2009 infection: two case-control studies, Spain, season 2009–2010. BMC Public Health. 2011;11:899.

Vesikari T, Virta M, Heinonen S, Eymin C et al. Immunogenicity and safety of a quadrivalent inactivated influenza vaccine in pegnant women: a randomized, observer-blind trial. Hum Vaccin Immunotherap. 2019;16:623−629.

Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med. 2008;359:1555–64.

RSV

Madhi SA, Polack FP, Piedra PA, Munoz FM, Trenholme AA et al. Respiratory syncytial virus vaccination during pregnancy and effects in infants. N Engl J Med. 2020;383:426−39.

Neonatal Immunization

Ener Cagri Dinleyici

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_7

7.1 Introduction

Neonatal immunization refers to the immunization of newborns during the first 28 postnatal days; however, neonatal immunization may also include vaccines used in the first 2 months of life and immunization practices among high-risk neonates, including preterm newborns.

Neonatal immunization represents a key global strategy in overcoming morbidity and mortality due to infection in early life. Neonatal immunization will provide early protection for neonates and infants, narrowing the critical and vulnerable duration between birth and before routine immunization schedules begin. With neonatal immunization, if an immunogenic response is elicited at this early stage, less vaccine doses may be required, as there may be a general immunomodulatory effect which improves immunity from birth until exposure to pathogens. Neonatal immunization can be easily implemented, considering that birth is a key point of communication with the global health system. Neonatal immunizations have not made the same progress as maternal immunizations, due to certain barriers and risks, including weak immunogenicity, safety concerns, and hypo-responsiveness to either the same antigen or concomitant antigens administered at birth or in subsequent months. The ideal vaccine for neonatal period will be delivered orally rather than via intramuscular or subcutaneous routes at birth (or before 4 weeks of age), safely eliciting a strongly protective response after a single dose with minimal interference with maternal antibodies. As part of the subsequent routine infant immunization schedule, this response will be sustained or easily boosted without developing hyporesponsiveness when confronted with the same or concomitant vaccine antigens.

7.2 Neonatal Immune System and Related Factors

The neonatal immune system is no longer considered immature, but rather precisely adapted for early postnatal life, developing over time through a regulatory process that has not yet been well defined. Mohr and Siegrist described the neonatal immune system as a response to danger signals and antigens characterized by anti-inflammatory rather than pro-inflammatory responses, leading to the preferential differentiation of CD4+ helper T cells (Th) to Th2 cells that antagonize Th1 cells and cytotoxic responses to intracellular pathogens, based on their propensity to differentiate into immunoregulatory cells. Immunological milieu is polarized towards Th2-type immunity with dampening of Th1-type responses and impaired humoral immunity, resulting in quantitatively and qualitatively poorer antibody responses compared to older infants. The efficacy of vaccines against the tuberculosis, hepatitis B, and oral polio is evidence of the concept that neonatal immunization can be used effectively.

The neonatal adaptive immune system is predominantly composed of naive lymphocytes during the intrauterine phase, indicating low exposure to foreign antigens. Dynamic changes in the maternal and fetal immune systems are necessary for a healthy pregnancy. After birth, the newborn and young infant's immune systems develop to meet the challenges of tolerance to commensal and immunity to infectious pathogens. The lack of cells encountered by antigens confers susceptibility to severe pathogens and leaves newborns reliant on their innate immune system. Functional deficiency in antigen-presenting cells is also demonstrated by innate immunity: the expression and signaling of toll-like receptors undergo maturational changes associated with different functional responses. This mechanism is biased against the activation of cytokine polarization of T helper 1 (Th1) cells, which is essential in preventing alloimmune reactions or excess anti-inflammatory reactions between mother and fetus but increases susceptibility to many viral and bacterial pathogens. In order to prevent the identification of the developing fetus as an allograft by the maternal immune system, the neonatal immunological environment is skewed towards T helper 2 (Th2) immunity, which poses a significant obstacle to vaccination during the neonatal era. Responses to

two main threat pathways in neonates, toll-like signaling of the receptor and interleukin (IL)-1/inflammasome pathways, are dampened and fail to induce potent pro-inflammatory responses, including IL-12p70, Th1 master cytokine, and cytotoxic responses. The low responsiveness of neonatal T cells to toll-like receptor and IL-1/inflammasome pathways has an impact on the intrinsic ability of T cells to respond to vaccines and pathogens. B-cell intrinsic and extrinsic features/limitations affect early-life humoral responses, but they are largely regulated by extrinsic factors. After birth, follicular dendritic cells grow slowly, delaying germinal cell formation, and bone marrow stromal cells have inadequate survival factors, such as a proliferation-inducing ligand. A major limiting factor for the growth of early-life germinal complex responses is the expansion of T follicular helper cells.

The quality and quantity of early infant antibody response are determined by several factors, including the stage of infant immune system development, the type of vaccine and its intrinsic immunogenicity, the number of doses and intervals between doses, and the effect of maternal antibodies. Most of the serum immunoglobulins of the newborn are derived from the transfer during the third trimester of pregnancy of maternal immunoglobulin G (IgG) through the placenta. Neonates and infants have a limited antibody repertoire, can produce suboptimal antibody responses to certain polysaccharides and protein antigens, and may demonstrate the limited persistence of these antibodies. The pathway of neonatal B-cell differentiation is skewed towards memory B cells rather than plasma cells. Increasing the placental transfer of maternal antibodies can effectively protect newborns and babies against such diseases, including tetanus, influenza, and pertussis. The amount of antibody transferred depend on several factors, including gestational age, maternal antibody level, type of IgG subclass, and placental characteristics. Maternal antibodies may interfere with infant vaccine responses, and also breast milk antibodies may affect the efficacy of vaccines. Concerns about the use of vaccines during the newborn period include the limited capacity of neonates to respond to many antigens and the potential effects of vaccinations on the immune system polarization during prenatal and early periods after birth. Immune components central to vaccine responses, including antigen-presenting cells, B cells, and T cells, function differently at birth than later in life. The implications of these complex changes on the efficiency of immune responses during pregnancy and soon after birth remain poorly understood. The advent of new technology and computational tolls allowing vast and complex data sets to be combined opens up new ways of understanding the immunobiology of the mother-infant dyad.

Maternal cofactors influencing immune ontogeny and immune responses in early life include chronic maternal infections, nutrition, the microbiome, and the levels and specificity of maternally acquired antibodies. Vaccines currently given at birth provide strong evidence that protective immunity can be induced by vaccination and can also inform on the potential of neonates to develop specific immune responses and on the impact of cofactors. There are three maternal factors that could theoretically influence the effectiveness of neonatal immunization: maternal-fetal antibody transmission, maternal-fetal pathogenic organism transfer, and recurrent maternal infections. Genetic variance between hosts, in addition to maternal influences, plays a key role in the observed variability of early responses to neonatal and infant vaccines. Another factor influencing the quantity and consistency of innate and adaptive responses is prematurity. Neonatal immunity and therefore vaccine responses often vary greatly across various geographical settings. The formation of gut microbiota, considered to be crucial for optimal host immune growth, is influenced by environmental factors combined with host genetics.

7.3 Neonatal Vaccines

The immunization studies have focused on the potential use of existing vaccines during the neonatal period, immunization practices in

premature babies, and new vaccines and adjuvants. The same immune deficiencies that render newborns susceptible to infection also reduce their memory responses to most antigens, thereby potentially frustrating efforts to protect this high-risk population. Some vaccines have been developed and proven safe and effective at birth. Three vaccinations are frequently used in neonates: the Bacillus Calmette-Guérin (BCG) vaccine, hepatitis B vaccines, and the oral polio vaccine (OPV). Recently, the use of neonatal rotavirus vaccines has also seen some promising results. As birth is the most reliable point of health-care contact worldwide and effective vaccination at birth would provide early protection for newborns and infants, expanding and improving the available means of neonatal vaccination are a global health priority.

7.4 BCG Vaccine

The BCG vaccine (see also ▶ Chap. 17) is a live attenuated *Mycobacterium bovis* vaccine that is usually administered intradermally within the first few days of life in most low- and middle-income countries to prevent tuberculous meningitis and miliary tuberculosis. Most infants receive the BCG vaccine at birth in accordance with World Health Organization (WHO) recommendations. The BCG vaccine is one of the most commonly used vaccines globally, with more than three billion people having received this vaccine, and the BCG vaccine exhibits an excellent safety profile. The protective efficacy of the neonatal BCG vaccine is 64–73% against meningitis and 77–78% against miliary tuberculosis. The effectiveness differs between countries, particularly against military tuberculosis and meningitis of tuberculosis, reflecting differential exposure to environmental mycobacteria, variations of the strain used in the BCG preparations, genetic or nutritional differences, and environmental factors such as exposure to sunlight and poor maintenance of the cold chain. The greatest benefit of BCG immunization has been observed in regions where both the risk of tuberculosis and the rates of vaccine coverage are highest.

The effectiveness of neonatal BCG vaccine administration has been linked to its ability to effectively induce neonatal immune responses that are polarized by anti-mycobacterial CD4+ T-cell Th1. BCG does not contain any exogenous adjuvant but is inherently "self-adjuvanted" because *Mycobacteria* induce immune responses via TLR2, TLR4, and TLR8. BCG vaccination at birth results in neonatal IFN-γ production against mycobacterial antigens, and the levels of secreted IFN-γ are comparable with adult levels. Notably, in early childhood, BCG also influences the immune response to unrelated antigens, enhancing both Th1- and Th2-type responses to other antigens (e.g., HBV and oral polio vaccines), possibly due to its effect on the maturation of dendritic cells (DC). Th1 responses are characterized by CD4+ T-cell interferon (IFN)-γ production. For combating infections with intracellular pathogens and toxin-producing species, enhanced neonatal Th1-polarized immune responses will be beneficial. Neonatal BCG vaccinations have demonstrated non-specific or heterologous effects against other unrelated infections, and it has also been reported to reduce neonatal and infant mortalities resulting from unrelated diseases. A meta-analysis of three BCG vaccine trials showed that early use of the BCG vaccine reduced mortality by 38% within the neonatal period and 16% by age 12 months. Cellular immunity measured at 10 weeks after BCG immunization was similar in infants administered BCG at birth and in those administered BCG at 2 months of age. These results suggest that delaying BCG immunization might not confer any immunological advantage in cellular immunity. Early administration of the BCG vaccine in low birth weight infants is also related to substantial reductions in mortality rates. The non-specific beneficial effects can also include reduction of atopic diseases (see ▶ Chap. 17). Although the underlying immunological mechanisms were not thoroughly elucidated, for these non-specific results, two theories were proposed: "trained innate immunity" and "heterologous immunity." The capacity of the innate immune system to produce immunological memory is defined by "trained innate immunity" and

thus trained to provide partial defense against subsequent infections, independent of classical T- and B-cell adaptive immunity.

Disseminated BCG infections are a major concern regarding the use of the BCG vaccine at birth. A disseminated BCG infection is a rare complication, occurring in less than one per million individuals, mainly those with congenital immune deficiencies. BCG vaccination at birth is no longer recommended in HIV-positive infants because of the risk of disseminated BCG disease, in approximately 1%, and the limited vaccine efficacy in HIV-infected infants.

The BCG vaccine is routinely recommended in Bulgaria, Hungary, Ireland, Latvia, and Lithuania at 48 h after birth without tests. In Poland, the BCG vaccine is administered within 24 h of birth. In Croatia, vaccination is ideally given at the time of hospital delivery; otherwise it should be given before 1 year of age. Vaccines in Cyprus and Luxembourg are administered only for particular indications at birth. In the Czech Republic, the BCG vaccine is given to babies in at-risk groups from the fourth day until 6 weeks after birth. In Estonia, BCG administration is recommended 1 to 5 days after birth. In Finland, France, Greece, and Malta, BCG vaccines are only given to specific groups at risk. In Romania, BCG vaccination is recommended 2 to 7 days after delivery. In Slovenia, vaccination is recommended for newborn infants of immigrant families who moved to Slovenia from countries with a high prevalence of tuberculosis in the last 5 years. Vaccination is recommended in the UK for infants and children who are particularly likely to come into contact with tuberculosis (see also ► Chap. 17).

7.5 Hepatitis B Vaccine

Primary prevention through immunization remains the most effective strategy for controlling the spread of the hepatitis B virus (HBV). One dose provides ~30–50 percent protection in healthy infants, two doses provide 50–75 percent protection, and three doses provide >90 percent infection protection from HBV. In the absence of antigen exposure/booster immunization, immunity elicited by neonatal/infant HBV immunization continues during life (see ► Chap. 13). Regardless of endemicity, the WHO recommends that the hepatitis B vaccine be given uniformly within 24 h of birth, followed by two or three additional doses of the vaccine. The first dose must be given within 7 days. The recommended birth dose schedule of the vaccine can eliminate most perinatally acquired infections and provide early protection against horizontal transmission. The hepatitis B vaccine induces at least equivalent antibody responses in newborns and adults; this suggests that the capacity of the newborn to develop antibody responses depends on the nature of the immune stimulus. The success of the HBV vaccine schedule confirms that, regardless of the primary antibody response, vaccination at birth can elicit potent memory B-cell responses that promote the immunogenicity of subsequent vaccine booster doses. It has been shown that the T-cell responses elicited by the HBV vaccine differ between newborns and adults; there are lower interferon-γ production (reflective of Th1 immunity) but higher Th2 memory responses compared to adults in those vaccinated at birth. In Europe, the first dose of the hepatitis B vaccine is recommended at 12 to 24 h after birth in Bulgaria, Poland, Portugal, Romania, and Turkey. Hepatitis B vaccination concurrently with hepatitis B immunoglobulin is recommended at birth for babies born to a mother infected with hepatitis B, and initial vaccination is given at birth. In 2017, the Advisory Committee on the Immunization Practices (ACIP) of the USA added monovalent hepatitis B vaccinations to all newborns within 24 h of birth. ACIP recommends the hepatitis B vaccine and hepatitis B immune globulin within 12 hours of birth for infants born to hepatitis B surface antigen (HBsAg)-positive mothers. The guidelines of the ACIP include the administration of the hepatitis B vaccine, irrespective of birth weight, if the status of the mother with HBsAg is uncertain.

7.6 Oral Poliovirus Vaccine (OPV)

An oral polio vaccine (OPV) is also recommended at birth as part of routine immunization in certain countries. The WHO also recommends an OPV dose at birth (called the "zero" dose) in polio-endemic countries and in areas at high risk for importation and eventual spread, followed by a primary sequence of three OPV doses with at least one IPV dose. OPV remains the first mucosal vaccine received by most newborns. Until April 2016, a trivalent OPV formulation was used worldwide, at which point it was substituted during a global coordinated switch with bivalent type 1 and type 3 OPV (see ► Chap 8).

7.7 Rotavirus Vaccine

A rotavirus vaccine provided at birth may provide early protection and could maximize the opportunity to complete a full vaccine schedule. In the early phase of the development of rotavirus vaccine, the use of a neonatal dose was investigated but was not followed due to concerns regarding legal issues related to safety.

The oral human neonatal rotavirus vaccine (RV3-BB) has been developed from the human neonatal rotavirus (RV3) strain (G3P[6]) found in the stools of infants with asymptomatic infections. In a phase 2a trial in New Zealand, when administered according to a neonatal or infant plan, RV3-BB was immunogenic and no safety issues were found. In Indonesia, a randomized, double-blind, placebo-controlled trial of RV3-BB found that healthy newborns received three doses (neonatal 0–5 days, 8 weeks, and 14 weeks of age) and the efficacy of the vaccine was 75%, compared with 51% in the child and 63% in the neonatal and infant combination groups, respectively. RV3-BB has been shown to have a vaccine efficacy of 94% at 12 months of age and 75% at 18 months of age when administered according to the neonatal schedule, findings that support the administration of RV3-BB starting from the time of birth.

The implementation of the rotavirus vaccine with a birth dose requires co-administration with other vaccines where available in newborn immunization schedules. Cowley and colleagues evaluated the co-administration of the RV3-BB and OPV, which are administered at birth in many developing countries. The two vaccines are oral vaccines, both of which replicating in the gut. Cowley and colleagues found that the responses of the poliovirus serum antibody and serum antibody titers to poliovirus 1, 2, and 3 were similar in newborns receiving RV3-BB co-administered with the OPV. The use of RV3-BB in a birth dose strategy is novel and has been shown to be effective in developing countries, but not yet adopted in practice.

7.8 Monovalent Acellular Pertussis Vaccine

In developed countries, the majority of deaths due to whooping cough occur in the first 2 months of life. The first clinical trial of the neonatal pertussis vaccine started in the 1940s but did not proceed due to subsequent concerns regarding immune tolerance and reduced responses in the presence of maternal antibody. A good safety profile was previously demonstrated by immunization within 24 h of life with whole cell pertussis or combined with diphtheria and tetanus vaccines; however, the serological response was suboptimal and a decreased response to pertussis boosters was recorded in 75 percent of study subjects up to 5 months of age, regardless of the low maternal antibody titer. Some studies have shown decreased responses to vaccines given concomitantly with the second dose of the pertussis vaccine. The activation of Th2-polarized cellular immune responses can be another disadvantage of pertussis immunization at birth. Immunization of neonatal pertussis may be suggested in babies born to mothers with low levels of Ab, decreased reaction to pertussis vaccine, or decreased transfer of maternal antibodies. In a randomized clinical trial in Australia, immunogenicity and safety from the birth dose of the monovalent acel-

lular pertussis (aP) vaccine were assessed between 2010 and 2013 in 440 healthy term infants of less than 5 days of age at recruitment. Of the babies receiving the aP vaccine at birth, 93.2 percent had detectable antibodies to both PT and pertactin at 10 weeks, while 50.8 percent had these antibodies in the control group.

To conclude, a birth dose aP vaccine is safe and well-tolerated and results in only nonsignificant decreases in antibody responses to some concomitantly administered vaccine antigens. Acellular pertussis vaccine administration at birth has the potential to decrease severe morbidity due to potential of pertussis infection in the first 3 months of life, especially in infants of mothers who have not received a pertussis vaccine during pregnancy. At this time, the neonatal pertussis vaccine is an alternative strategy for infants when their mothers have not been vaccinated, although maternal vaccination would be a better choice (see ► Chap. 6).

7.9 Pneumococcal Vaccine

There are limited studies about the use of pneumococcal conjugated vaccines with a birth dose. In Kenya, the use of the seven-valent conjugate vaccine (PCV7) at birth (with 10 and 14 weeks) appears to be safe, and there was no substantial difference in the proportion of IgG above the protective threshold for each serotype at 18 and 36 weeks compared to the routine infant regimen, whereas the geometric mean concentrations for some serotypes in the birth dose group were lower. Response to 36-week boosters and vaccine-type/non-vaccine-type carriage prevalence were comparable between groups, suggesting absence of immunological tolerance after schedule including birth dose. PCV7 was administered in Papua New Guinea on a 0–1-2-month (neonatal) cycle with a 23-valent pneumococcal polysaccharide vaccine booster at the age of 9 months. Although all antibody responses to vaccine forms in the birth dose group were not lower than those in the infant group at 2 months of age, the infant-immunized group typically had higher antibody levels over time than the neonatal-immunized group. There is also no birth dose tolerance for PCV7 in this research. However there are no routine recommendations for birth dose for PCVs.

7.10 Immunization of Premature Infants

It is generally recommended that premature infants should follow the same vaccination schedule that is generally used for full-term infants, without correcting for prematurity and regardless of birth weight. The routine immunization of premature infants, however, is frequently delayed because many clinicians suspect that these infants' compromised immune systems could substantially suppress responses to vaccine antigens and minimize the vaccination's protective effects. Preterm infants have lower than normal maternal IgG concentrations, resulting in increased susceptibility to infection, including pertussis, pneumococcus, rotavirus, influenza, and RSV. This is in part also due to reduced cellular immune responses and lower lymphocyte counts, as well as lower levels of maternal antibodies. Preterm infants are frequently excluded from new vaccine prelicensing trials, effectiveness studies are almost non-existent, and immunogenicity studies contain small numbers, different schedules, and different populations with differing requirements for inclusion and exclusion, posing a barrier for this group in evidence-based decision-making. Preterm infants typically have lower antibody concentrations after primary vaccinations than full-term infants, but proportions achieving protective concentrations may be equivalent for vaccines for which correlates of protection have been described. In these infants, booster doses are particularly important. Potential post-immunization adverse events, such as apnea and major cardiorespiratory events, occur more often in preterm infants than in full-term infants, but, overall, vaccinations are safe in preterm infants who should be immunized in accordance with their chrono-

logical age rather than their adjusted gestational age.

Numerous differences in vaccine responses between premature and full-term newborns have been observed. Less than sufficient amounts of peptides are secreted by skin, lung, and epithelial cells, such as defensins, which can alter gene expression, act as chemokines and/or induce chemokine production, inhibit the production of pro-inflammatory cytokine-induced lipopolysaccharides, and modulate the responses of dendritic cells and adaptive immune response cells. For premature newborns, an impaired innate system is another important factor for immunization via antigen-presenting cell dysfunction resulting from suboptimal vaccine responses. Adaptive cellular and humoral immunity is also less efficient in premature newborns, including the suboptimal functioning of Th1 and Th2 polarized responses with the relative impairment of Th1 activity, significantly reduced T-cell repertoire limiting the recognition of the peptides, less IL-2 production, decreased cytolytic activity, and abnormal cytokine production associated. Premature infants predominantly respond with IgM, and there is a slow or no switch to IgG. Maternal antibodies are lower in premature babies than in infants, which could potentially enhance vaccine responses. Clinical studies have shown that premature infants seroconvert in response to the hepatitis B vaccine by 30 days of age, regardless of gestational age and birth weight, suggesting that prematurity per se rather than gestational age or birth weight might be more predictive of a decreased antibody response.

Babies born at under 32 weeks of gestation or with a birth weight of under 2000 g are advised to receive their hepatitis B vaccines at 0, 2, 4, and 6 months of age followed by either a test for hepatitis B antibodies at 7 months of age and a booster at 12 months of age if the titer of the antibody is <10 mUnits/mL or give a booster at 12 months without measuring the titer of the antibody. Recent systematic review evaluated the immunogenicity and the safety of BCG vaccine in preterm and/or low birth weight neonates which were vaccinated in the first 7 days. There is no difference in the incidence of death, systemic disease, scar formation, and immunogenicity. Based on their findings, they recommended early BCG vaccination in stable infants who are preterm and/or have low birth weight to improve uptake. The immunogenicity of the meningococcal C-conjugated vaccine in premature infants is not different from that of full-term infants. Most studies on the *Haemophilus influenzae* type b vaccine reported only marginal differences between premature and full-term infants. This finding clearly indicates that most premature infants, particularly those at a gestational age > 32 weeks, remain protected, even after the primary series. Premature infants are at an increased risk for invasive pneumococcal disease compared with term infants and are more likely to have lower vaccine responses compared with term infants. A recent clinical study that included 210 premature newborns showed that after primary PCV13 vaccination, 75%, 88%, and 97% of participants had protective antibody concentrations for at least one-half of the PCV13 serotypes for the reduced, accelerated, and extended schedules, respectively. After the booster vaccination, nearly all participants, regardless of schedule or serotype, had seroprotective IgG concentrations. A reduced priming schedule for PCV13 resulted in higher post-booster IgG concentrations, but lower post-primary concentrations. Preterm infants are vulnerable to severe rotavirus infection resulting in hospitalization. Rotavirus vaccines are immunogenic and safe and have been demonstrated to have similar effects in preterm infants to term infants when given according to calendar age. However, preterm newborns are usually not given rotavirus vaccine at birth but only at a calendar age of 6–8 weeks.

Overall, premature infants should follow the same vaccination schedule as that generally used for full-term infants, without correcting for prematurity and regardless of birth weight. Even though an impaired immune response can reduce antibody production and cell-mediated immunity, antibody production is high enough to ensure short- and long-term protection in most premature infants. Maternal immunization is a crucial mechanism by which these highly vul-

nerable infants may be covered, given that vaccination takes place in the second trimester and that a significant transfer of antibodies is accomplished prior to birth, although this benefit will not carry for extremely vulnerable preterm infants.

7.11 The Need for Novel Approaches to Enhancing Neonatal Vaccination

There are three innovative approaches to neonatal immunization: new types of vaccine configurations (both modes of action and antigen-adjuvant formulations vary), new types of delivery for vaccines, and new types of strategies for infant immunization. Adjuvants boost infant immunity via multiple mechanisms: triggering inherent immune responses; increasing the half-life of the vaccine antigen by producing a "depot effect"; assembling and directing antigens to antigen-presenting cells (APCs) and then activating them; generating stronger mucosal responses; and fostering cell-mediated immunity by improving the role of cytotoxic or Th-1 form T cells. Adjuvants strengthen neonatal vaccine immunogenicity through innate activation and through the enhancement of multiple aspects of adaptive immunity. Adjuvants, such as monocytes and dendritic cells, can activate APCs and increase the development of cytokine and co-stimulatory marker expression, which enhances the priming of naive CD4+ T cells. CD4+ T cells can differentiate into T follicular helper cells after activation and antigen presentation, which are essential in the germinal center reaction to assist B cells in generating effective antibodies. Improvement in memory and plasma B cells increases the identification and neutralization of antigens by increasing the production of antibodies of high affinity.

Novel adjuvants are an exciting area of neonatal immunizations. Much interest has focused on specifically stimulating TLR3, TLR7, TLR8, and TLR9 receptors, which are located within endosomes and display robust responses to stimulation in neonates. It has been shown that pertussis toxoid-specific antibody secretion has been increased by CpG DNA, a TLR9 ligand. Similarly, TLR8 agonists, such as some synthetic imidazoquinolines and single-stranded viral RNA, are especially effective in stimulating in vitro human neonatal APCs, eliciting secretion of TNF and IL12p40/70 and promoting upregulation of the CD40 co-stimulatory molecule. Recently, TLR8 agonist nanoparticles (polymersomes) mimic immunomodulatory mechanisms with higher IL12p70 secretion seen after BCG administration. In particular, the ability to concurrently stimulate multiple TLRs has a synergistic effect, with a recent emphasis on combined stimulation of TLR7/TLR8 to bypass impairment of APC responses in newborns. Simultaneously ligating both TLR7 and TLR8 receptors, R848 is especially effective in activating human neonatal APC in vitro, resulting in more pronounced TNF alpha and IL-1β production than when individually stimulated at these sites. When administered to rhesus macaques on the first day of life, a lipidized TLR7/8 agonist has been reported to enhance B-cell responses to a polysaccharide pneumococcal vaccine. Some combinations of STING and TLR agonists function in synergy to cause Th1-polarizing responses from human neonatal antigen-presenting cells, indicating that STING agonists may be candidate adjuvants for early life immunization, alone or in combination with alum and/or TLR agonists. There are limited studies on the effects of TLR adjuvants, with most neonatal data still coming from neonatal animal models on novel adjuvants, with uncertainty as to how well the situation in human neonates could reflect this. Recently, sugar-like structures have been shown to prime the adaptive immune system for infants to respond to vaccines, possibly being more successful than conventional adjuvants. In neonatal vaccine models, sugar-based compounds with beneficial adjuvant effects include delta inulin and curdlan. Such compounds, either used alone or in conjunction with conventional innate immune adjuvants, make potential neonatal adjuvant candidates.

Experimental studies have indicated that antigen entry into the cytoplasm of APCs is a crucial condition for the induction of an efficient neonatal adaptive response. Neonatal immune responses can be enhanced by the cytoplasmic delivery of antigens. An attenuated strain of the intracellular pathogenic bacterium *Listeria monocytogenes* has used a novel approach to neonatal vaccination to transmit antigens to the APC cytoplasm. Another approach is fostering the robust response of T cells, including transferring polarization to immunity of type Th1. In mediating DC-directed T-cell differentiation to TFH, interleukin-12 is essential and co-administration of IL12 and influenza subunit vaccine to newborn mice has resulted in the improved protective efficacy of antiviral immunization.

Administration of neonatal vaccines through the mucosal route will be an option for increasing their efficacy. Experimental studies on intranasal administration of the candidate RSV vaccine at birth can, even in the presence of high RSV-specific maternal antibody titers, elicit systemic humoral immune responses and elevated IFNγ secretion. In order to improve immune responses to homologous or heterologous boosters in later childhood, there are also several hybrid methods, such as using neonatal vaccines as primers.

7.12 COVID-19

Concerns about the risk of vertical or perinatal transmission of SARS-CoV-2 and the impact of the infection on the pregnant woman, the fetus, or the infant have been posed during the current COVID-19 pandemic. In newborns, the incidence and complications of COVID-19 tend to be relatively mild. A recent systematic analysis of neonatal COVID-19 infections showed that 71% were confirmed/probably postnatally acquired, 3.3% were intrapartum acquired (with an additional 14% likely/possibly intrapartum acquired), and 5.7% were confirmed congenital cases (with an additional 6.5% likely/possibly congenital). There is no current clinical trial of the proposed newborn COVID-19 vaccine and no evidence on the normal use of these candidates in infants. Due to the potential for non-specific (heterologous) immunomodulatory effects resulting in defense against a variety of infections, BCG remains a significant interest, as postulated for COVID-19, but there is no routine recommendation for the BCG vaccine for the potential prevention of COVID-19. WHO recommended that the existing evidence was insufficient to prompt a revision of immunization policy including the prevention of COVID-19.

There are tremendous scientific activities underway to achieve safe and efficient vaccines and new immunization methods, including mRNA vaccines, adenovirus vector-based vaccines, or protein subunit vaccines, and these have been reported with encouraging results. Experience with these technologies and lessons learned from COVID-19 vaccine would be an option for potential neonatal vaccines. The evaluation of vaccine-preventable disease epidemiology and routine neonatal immunization records should be a priority for all countries during and after the pandemic.

7.13 Conclusion

Maternal and neonatal immunization is an effective key strategy in reducing death and significant morbidity from infectious diseases globally. A significant goal of global interaction with health care is the production of early life vaccinations, including vaccines that are safe when administered at birth. Even in the presence of maternal antibodies, an ideal vaccine for neonatal period would induce a rapid immune response and would have an optimal safety profile. Despite the difficulties inherent in the production of vaccines for newborns, there is a clear reason for continued vaccine development for this population, including the fact that birth is the most secure point of contact with health care. Newborn vaccines are also a valuable and secure probe for neonatal immunity that create a more

thorough understanding of protective mechanisms in early life by allowing the controlled delivery of a well-defined immune challenge to the naive newborn immune system. There is a common practice of neonatal immunization against tuberculosis, hepatitis B, oral polio virus vaccine, and some promising recent rotavirus vaccine findings. Considering the potentially significant benefit of vaccinating at birth, the availability of a broader range of more effective neonatal vaccines is an unmet medical need and a public health priority. In future studies, lessons from early immune ontogeny must be incorporated, and focus must be on the creation of vaccine types with novel mechanisms of action that associate with the distinctive neonatal immune profile. Innovative neonatal vaccines must also undergo both comprehensive safety tests and human clinical trials.

Further Reading

Andersen P, Doherty TM. The success and failure of BCG – implications for a novel tuberculosis vaccine. Nat Rev Microbiol. 2005;3:656–62.

Badurdeen S, Marshall A, Daish H, Hatherill M, Berkley JA. Safety and Immunogenicity of Early Bacillus Calmette-Guérin Vaccination in Infants Who Are Preterm and/or Have Low Birth Weights: A Systematic Review and Meta-analysis. JAMA Pediatr. 2019;173(1):75–85.

Berrington JE, Barge D, Fenton AC, Cant AJ, Spickett GP. Lymphocyte subsets in term and significantly preterm UK infants in the first year of life analysed by single platform flow cytometry. Clin Exp Immunol. 2005;140(2):289–92.

Biering-Sørensen S, Aaby P, Lund N, Monteiro I, Jensen KJ, Eriksen HB, Schaltz-Buchholzer F, Jørgensen ASP, Rodrigues A, Fisker AB, Benn CS. Early BCG-Denmark and Neonatal Mortality Among Infants Weighing <2500 g: A Randomized Controlled Trial. Clin Infect Dis. 2017;65(7):1183–1190.

Bines JE, At Thobari J, Satria CD, Handley A, Watts E, Cowley D, Nirwati H, Ackland J, Standish J, Justice F, Byars G, Lee KJ, Barnes GL, Bachtiar NS, Viska Icanervilia A, Boniface K, Bogdanovic-Sakran N, Pavlic D, Bishop RF, Kirkwood CD, Buttery JP, Soenarto Y. Human Neonatal Rotavirus Vaccine (RV3-BB) to Target Rotavirus from Birth. N Engl J Med. 2018;378(8):719–730.

Bonhoeffer J, Siegrist CA, Heath PT. Immunisation of premature infants. Arch Dis Child. 2006;91(11):929–35.

Chaudhari T. Vaccinations in the newborn. Best Pract Res Clin Obstet Gynaecol. 2020 Oct 13:S1521–6934(20):30156–5.

Cowley D, Sari RM, Handley A, Watts E, Bachtiar NS, At Thobari J, Satria CD, Bogdanovic-Sakran N, Nirwati H, Orsini F, Lee KJ, Kirkwood CD, Soenarto Y, Bines JE. Immunogenicity of four doses of oral poliovirus vaccine when co-administered with the human neonatal rotavirus vaccine (RV3-BB). Vaccine. 2019;37(49):7233–7239.

Cuenca AG, Wynn JL, Moldawer LL, Levy O. Role of innate immunity in neonatal infection. Am J Perinatol. 2013;30(2):105–12.

Demirjian A, Levy O. Neonatal vaccination: a once in a lifetime opportunity. Pediatr Infect Dis J. 2009a;28(9):833–5.

Demirjian A, Levy O. Safety and efficacy of neonatal vaccination. Eur J Immunol. 2009b;39(1):36–46.

Dinleyici EC, Borrow R, Safadi MAP, van Damme P, Munoz FM. Vaccines and routine immunization strategies during the COVID-19 pandemic. Hum Vaccin Immunother. 2020;17(2):400−7.

Esposito S, Fumagalli M, Principi N. Immunogenicity, safety and tolerability of vaccinations in premature infants. Expert Rev. Vaccines. 2012;11(10):1199–209.

Fine PE. Variation in protection by BCG: implications of and for heterologous immunity. Lancet. 1995;346:1339–45.

Gagneur A, Pinquier D, Quach C. Immunization of preterm infants. Hum Vaccin Immunother. 2015;11(11):2556–63.

http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx

https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf.

Kilich E, Sadarangani M. Use of rotavirus vaccines in preterm babies on the neonatal unit. Expert Rev. Vaccines. 2016;15(12):1463–5.

Levy O. Innate immunity of the newborn: basic mechanisms and clinical correlates. Nat Rev. Immunol. 2007;7:379–90.

Libraty DH, Zhang L, Woda M, Acosta LP, Obcena A, Brion JD, Capeding RZ. Neonatal BCG vaccination is associated with enhanced T-helper 1 immune responses to heterologous infant vaccines. Trials Vaccinol. 2014;3:1–5.

Linterman MA, Hill DL. Can follicular helper T cells be targeted to improve vaccine efficacy? F1000Res. 2016;5.

Mohr E, Siegrist CA. Vaccination in early life: standing up to the challenges. Curr Opin Immunol. 2016;41:1–8.

Morris MC, Surendran N. Neonatal vaccination: challenges and intervention strategies. Neonatology. 2016;109(3):161–9.

Munoz FM, Van Damme P, Dinleyici E, Clarke E, Kampmann B, Heath PT, Levy O, Leuridan E, Cutland C, Sobanjo-Ter Meulen A, Marchant A. The Fourth International Neonatal and Maternal Immunization Symposium (INMIS 2017): Toward

Integrating Maternal and Infant Immunization Programs. mSphere. 2018;3(6):e00221–18.
Munoz FM. Can We Protect Pregnant Women and Young Infants From COVID-19 Through Maternal Immunization? JAMA Pediatr. 2021 Jan 29. https://doi.org/10.1001/jamapediatrics.2021.0043.
Sadarangani M, Kollmann T, Bjornson G, Heath P, Clarke E, Marchant A, Levy O, Leuridan E, Ulloa-Gutierrez R, Cutland CL, Kampmann B, Chaithongwongwatthana S, Dinleyici E, van Damme P, Munoz FM. The Fifth International Neonatal and Maternal Immunization Symposium (INMIS 2019): Securing Protection for the Next Generation. mSphere. 2021 Jan 27;6(1):e00862–20.
Sakala IG, Eichinger KM, Petrovsky N. Neonatal vaccine effectiveness and the role of adjuvants. Expert Rev. Clin Immunol. 2019;15(8):869–878.
Saso A, Kampmann B. Vaccine responses in newborns. Semin Immunopathol. 2017;39(6):627–642.
Scott JA, Ojal J, Ashton L, Muhoro A, Burbidge P, Goldblatt D. Pneumococcal conjugate vaccine given shortly after birth stimulates effective antibody concentrations and primes immunological memory for sustained infant protection. Clin Infect Dis. 2011;53(7):663–70.
Siegrist CA. The challenges of vaccine responses in early life: selected examples. J Comp Pathol. 2007;137(Suppl 1):S4–9.
Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. Proc Biol Sci. 2015;282(1821):20143085.
Stensballe LG, Ravn H, Birk NM, Kjærgaard J, Nissen TN, Pihl GT, Thøstesen LM, Greisen G, Jeppesen DL, Kofoed PE, Pryds O, Sørup S, Aaby P, Benn CS. BCG Vaccination at Birth and Rate of Hospitalization for Infection Until 15 Months of Age in Danish Children: A Randomized Clinical Multicenter Trial. J Pediatric Infect Dis Soc. 2019;8(3):213–220.
Stensballe LG, Sørup S, Aaby P, Benn CS, Greisen G, Jeppesen DL, Birk NM, Kjærgaard J, Nissen TN, Pihl GT, Thøstesen LM, Kofoed PE, Pryds O, Ravn H. BCG vaccination at birth and early childhood hospitalisation: a randomised clinical multicentre trial. Arch Dis Child. 2017;102(3):224–31.
Swaminathan S, Rekha B. Pediatric tuberculosis: global overview and challenges. Clin Infect Dis. 2010;50(Suppl 3):S184–94.
van den Biggelaar AH, Pomat W, Bosco A, Phuanukoonnon S, Devitt CJ, Nadal-Sims MA, Siba PM, Richmond PC, Lehmann D, Holt PG. Pneumococcal conjugate vaccination at birth in a high-risk setting: no evidence for neonatal T-cell tolerance. Vaccine. 2011;29(33):5414–20.
van den Ende C, Marano C, van Ahee A, Bunge EM, De Moerlooze L. The immunogenicity of GSK's recombinant hepatitis B vaccine in children: a systematic review of 30 years of experience. Expert Rev. Vaccines. 2017;16(8):789–809.
Wood N, Nolan T, Marshall H, Richmond P, Gibbs E, Perrett K, McIntyre P. Immunogenicity and Safety of Monovalent Acellular Pertussis Vaccine at Birth: A Randomized Clinical Trial. JAMA Pediatr. 2018;172(11):1045–1052.

Viral Vaccines and Vaccinations

Contents

Poliovirus Vaccines

Tapani Hovi and Timo Vesikari

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_8

8.1 The Disease

Acute anterior poliomyelitis was recognized as a clinical entity in the late nineteenth century and was shown to be caused by a virus in the early twentieth century. Initially, it was considered to be mainly a disease of young children, hence the old name "infantile paralysis." Frequent large outbreaks through the Western world during the first half of the twentieth century – together with individual adult victims of the disease among persons with powerful positions in the USA – increased the interest in research and facilitated its funding. There were about 35,000 cases of paralytic polio annually in the USA before the introduction of vaccination in the mid-1950s.

Development of the cell culture techniques and propagation of polioviruses in the late 1940s enabled detailed studies of the disease, confirmation of the diagnosis by virological laboratory tests, and, eventually, development of vaccines. Polioviruses are small, non-enveloped RNA viruses belonging to the family *Picornaviridae*, genus *Enterovirus*. Polioviruses infect only cells and tissues of humans or other primates, and humans are the only natural hosts of the virus. Polioviruses are divided into three distinct serotypes, referred to as poliovirus types 1, 2, and 3. Two types of poliovirus vaccines, an inactivated whole virion vaccine (IPV) and an orally administered, live attenuated poliovirus vaccine (OPV), have been available since the late 1950s and early 1960s, respectively. Systematic use of the vaccines has eliminated polioviruses from circulation in human populations in most parts of the world, thanks to the Global Polio Eradication Initiative (GPEI), established by the World Health Assembly in 1988. The last cases in Europe were reported in 1996 in Albania, Greece, and Kosovo and 1998 in Turkey. However, even with this rarity of new cases, the maintenance of immunity to poliovirus will still be important for years to come, as discussed in detail below.

8.1.1 Pathogenesis and Symptoms

The virus enters the body in contaminated food or via close physical contacts to infected persons or their excreta. Primary virus replication takes place in the oropharyngeal or intestinal mucosa, and the virus then spreads to submucosal lymphatic tissues. This phase of the infection may present with nonspecific symptoms of acute infection. The virus is shed in the excreta of the oropharynx during the first 2 weeks of infection, and in the stools for several weeks, up to a couple of months (Fig. 8.1). From the lymphatic tissues, the virus may enter the blood circulation and thereby reach secondary replication sites, including the oropharynx and the central nervous system (CNS). In the CNS, the most common but not exclusive target tissue is the medullary anterior horn (hence the full name, *acute anterior poliomyelitis*). Apart from crossing the blood–brain barrier, a viral route into the CNS can be initiated through mechanical damage of the axons of the motor neurons, for instance, by intramuscular injections and subsequent retrograde transport of the virus into the soma of the neuron. Lytic infection of the upper motor neurons results in rapid paralysis of the corresponding muscular fibers in the skeletal muscles. In the more severe forms of poliomyelitis, the bulbar nuclei are involved, and destruction of those regulating respiration and circulation may result in death.

Only 0.2–1% of immunologically naive individuals who are infected develop paralytic symptoms. The "typical" paralytic presentation of the disease could thus be considered a complication of the infection that is largely asymptomatic or associated with mild nonspecific symptoms of common acute infection. Acute mortality of paralytic patients is about 10%. Of the survivors, about one third recover to become symptom-free within a few months; another third have lifelong sequelae complicating mobility and skeletal development; and the rest live with milder, persisting symptoms. No specific treatment is available.

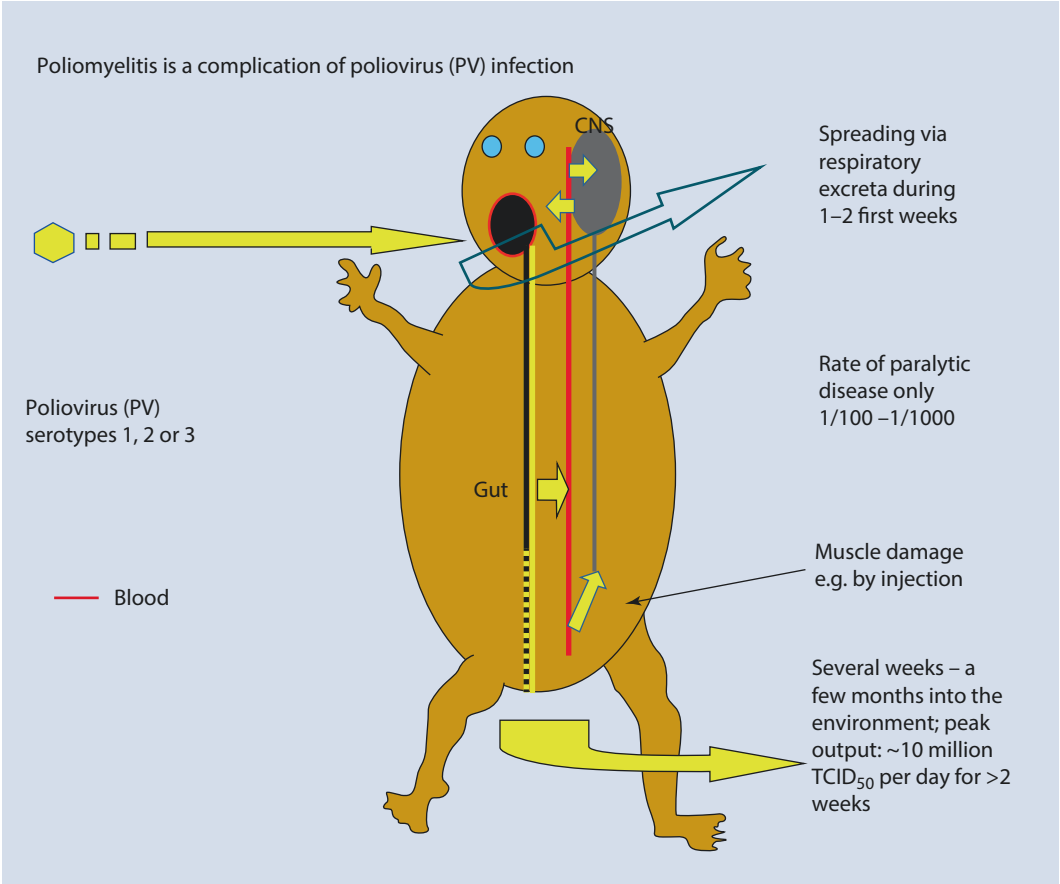


Fig. 8.1 Schematic picture of poliovirus infection

8.1.2 Immunity

An immune response follows the natural course of poliovirus infection irrespective of associated clinical symptoms. Both virus-specific class IgM, IgA, and IgG antibodies appear in the circulation, and class IgA antibodies are excreted in oropharyngeal and gastrointestinal mucosa. Intestinal IgA antibodies are crucial for protection against reinfection of individuals and for the limitation of virus transmission in the population (herd immunity). Levels of IgM and IgA decay within months, whereas the neutralizing class IgG response gives lifelong protection from paralytic disease. A cellular immune response can be demonstrated, but its potential role in the recovery, initial virus elimination, and later protective immunity is not well understood. The neutralization activity of the antibodies is type-specific, and a person surviving paralytic poliomyelitis caused by, say, type 1 poliovirus remains susceptible to type 2 and type 3 poliovirus infection and, in principle, could fall ill with a second episode of poliomyelitis.

8.2 Inactivated Poliovirus Vaccine

The inactivated poliovirus vaccine (IPV), also referred to as the killed poliovirus vaccine (KPV), was developed in the 1950s by Jonas Salk and his colleagues in the USA. The original Salk vaccine contained representatives of all three poliovirus strains, wild neurovirulent strains PV1/Mahoney, PV2/MEF-1, and PV3/Saukett, inactivated by a low concentration of formalin. Protective efficacy of the vaccine was demonstrated in large field studies (USA, Canada, Finland), and from 1957, several

European countries started to use the vaccine for the immunization of children and older age cohorts in the population. A few countries (Sweden, Finland, Norway, Iceland, the Netherlands) capable of reaching high vaccination coverage succeeded in eliminating poliomyelitis using this vaccine and continued to use IPV exclusively. With sub-optimal coverage levels, however, poliovirus transmission and outbreaks continued, although at highly reduced levels. Most European countries subsequently switched to the use of the oral, attenuated poliovirus vaccine when it became available.

New techniques for virus propagation, virion purification, and vaccine manufacturing were worked out in the early 1980s at the Dutch Institute for Public Health and Environment (RIVM) by Anton van Wezel and coworkers. All currently available IPV preparations are based on these manufacturing principles. Antigenic stability of the vaccine is guaranteed by using only a standard, limited number of virus passages to create the infectious seed for individual vaccine bulk production. The cell substrate for virus propagation is a well-characterized Vero cell subline or the diploid human embryonic lung cell line MRC-5. Growth of the cells on microcarriers enables large-scale fermenter-based manufacturing of the vaccine (Fig. 8.2). After infection, the virus is purified from the supernate by gel filtration and ion exchange chromatography and is inactivated by careful incubation in 3 mM formaldehyde. Standardized procedures are important because it is known that the antigenic phenotype of purified poliovirus may be changed from the neutralizing antibody-inducing D-type to the non-inducing C-type. Antigenicity of IPV is expressed in so-called D-units (DU). Typically, trivalent IPV preparations contain uneven amounts of the three serotypes, the original van Wezel version 40:8:32 DU of poliovirus types 1, 2, and 3, respectively. These serotype ratios were selected for their optimally balanced immune response toward all three serotypes. IPV-only vaccine preparations do not contain any adjuvant, but all the currently used pediatric combination vaccines contain aluminum adjuvant.

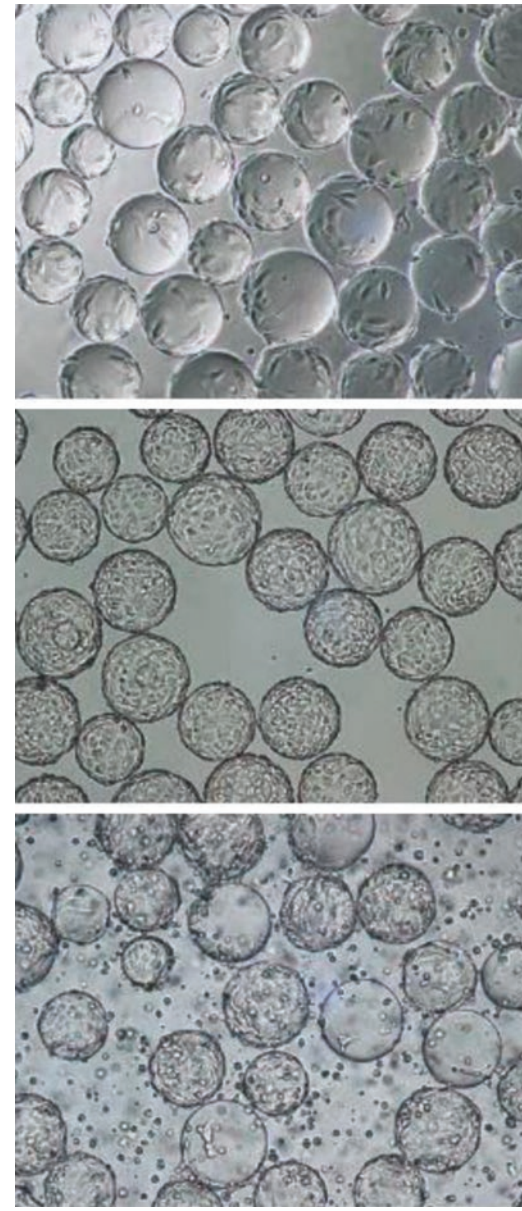


Fig. 8.2 Growth of Vero cells on microcarrier particles and the effect of poliovirus infection on cells. *Upper panel,* cells soon after; *middle panel*, cells grown to confluence a couple of days before virus inoculation; *lower panel*, cytopathic effect of poliovirus before harvest (captured from a GE brochure of cell culture equipment)

Seronegative infants seroconvert rapidly to all three poliovirus serotypes after two injections of IPV with an interval of 1 month or more between the doses. Additional doses further increase the antibody concentration in circulation. The formalin inactivation of

polioviruses is known to destroy some of the several antigenic determinants involved in the induction of neutralizing antibodies. Yet, IPV-induced immunity gives full protection against paralytic poliomyelitis. Originally, Salk and coworkers suggested that two or three doses of the new "enhanced potency" IPV suffice to induce long-lasting immunity to all three poliovirus serotypes. Yet, the pediatric immunization schedules usually include four or five doses of IPV.

Inactivated poliovirus vaccine alone does not induce significant intestinal IgA response and thus is considered inferior to the oral poliovirus vaccine in inducing protection against intestinal reinfection and in creating herd immunity in human populations. IPV injections to previously OPV-immunized individuals strongly boost the intestinal immunity.

Inactivated poliovirus-induced circulating antibodies can also prevent the post-viremic secondary replication of the virus in the oropharynx and thus interfere with the further spread of infections in the population. Oropharyngeal shedding of poliovirus is likely to play a major role in poliovirus transmission under the Western-style hygienic conditions where the classical feco-oral transmission route is partly blocked by well-organized sanitary systems.

The IPV-only vaccine preparations can be administered using intramuscular or subcutaneous injections, whereas the pediatric combination vaccines containing IPV are recommended for intramuscular use only. Adverse effects due to IPV administration are rare and, if they do occur, are limited to common inconveniences and local reactions at the injection site.

After elimination of wild-type polioviruses in Europe, OPV-using countries have returned one by one to the IPV-only immunization programs using the new IPV. France made this switch during the 1990s and the UK in 2004. At present, all Western European use IPV only in primary immunizations.

Although several European vaccine manufacturers make IPV, most of the IPV used is given as the pediatric combination vaccines, and the availability of IPV-only preparations needed for optional boosters for individuals exposed to poliovirus has occasionally been limited.

► https://www.vaccineshoppecanada.com/document.cfm?file=IMOVAX_Polio_E.pdf.

8.3 Oral Poliovirus Vaccine

Selected isolates from each of the three serotypes of poliovirus were serially passaged in monkeys or in cell 3. Oral poliovirus vaccine (OPV) cultures and the desired attenuation were monitored by designated neurovirulence tests in monkeys in vivo. Out of the few candidates, a set of strains developed by Albert Sabin and colleagues was finally chosen for wider studies on efficacy and safety in infants. The strains are pragmatically referred to as PV1/Sabin, PV2/Sabin, and PV3/Sabin, or Sabin 1, Sabin 2, and Sabin 3, respectively. The largest field study was carried out in the Soviet Union (including Estonia, Latvia, and Lithuania) during the late 1950s and early 1960s. The trivalent OPV was shown to be highly effective, and the frequency of harmful effects (vaccine-associated polio) was considered acceptable compared with the threat of the devastating disease. The vaccine was relatively inexpensive, and oral administration did not require specially trained healthcare personnel. Hence, most national immunization programs rapidly adopted OPV for use in all infants.

The relative proportions of poliovirus serotypes in the vaccine formulation were found to be important to guarantee seroconversion to all three serotypes. Typically, a dose of OPV included 10^6 cell culture infectious units (CCU_{50}) of PV1/Sabin, 10^5 CCU_{50} PV2/Sabin, and 3×10^6 CCU_{50} of PV3/Sabin (10:1:3 ratio). Replication of the attenuated polioviruses in the epithelia and submucosa of the intestines results in shedding of the virus into stools and induction of both circulating neutralizing antibodies and local (intestinal) IgA antibodies. The local immune response is considered to be crucial for resistance to intestinal reinfection and for the herd immunity in immunized populations.

Wider use of OPV in the early 1960s soon revealed that vaccine-associated paralytic poliomyelitis (VAPP) may occur in the vaccinee or in a contact. The frequency of VAPP is about 1 case in 700,000 primary vaccinations. Earlier vaccine doses, either OPV or IPV, decrease the risk. In Denmark, this observation was exploited by establishing a safe combination schedule for polio immunizations, starting with three doses of IPV and followed by three doses of OPV.

Most VAPP patients shed either type 2 or type 3 poliovirus related to the corresponding OPV component. Sabin 2 virus is genetically close to the wild parental virus. Sabin 3 shows only 10 point mutations, differentiating it from the parental PV3/Leon strain, whereas Sabin 1 has 57 single nucleotide differences compared with the parental PV1/Mahoney strain. During a few days of replication of the OPV-derived viruses in the human body, the viruses are readapted to human tissues, lose many of the attenuating mutations, and revert to neurovirulence. Although VAPP was initially accepted as the price of an inexpensive and effective immunization program, it later became intolerable in the absence of wild poliovirus transmission and with decreasing risks of importation of wild polioviruses. Thus, one after another, European countries stopped using OPV in routine immunizations and switched to programs using various pediatric combination vaccines including IPV components.

Researchers have long ago developed genetically modified derivatives of the Sabin strains which are less likely to revert to neurovirulence than the original Sabin strains. So far, they have not been used in human immunizations.

In the early 1960s, OPV-derived polioviruses were also shown to be able to spread from the primary vaccinees to close contacts, a feature initially considered beneficial by improving the nominal coverage of the vaccination. The shift of the millennium marked a significant change in the safety consideration of this phenomenon. An outbreak of paralytic poliomyelitis on the Caribbean island of Hispaniola in 2000 and several similar ones subsequently discovered in different parts of the world with low OPV coverage showed that OPV-derived polioviruses of any serotype may circulate, genetically revert to virulence, and behave like wild polioviruses. These viruses are referred to as circulating vaccine-derived polioviruses (cVDPV).

► http://www.epid.gov.lk/web/images/pdf/Polio/switch_plan_sri%20lanka_updated_nov%202015.pdf.

8.4 Global Poliovirus Eradication Initiative

8.4.1 Background and Current State

In the 1970s, the WHO had incorporated OPV into the six-disease-target Expanded Programme of Immunization recommended to all infants worldwide. The coverage of the age-based immunization remained low in developing countries. In the Americas, the Pan American Health Organization started to supplement the routine vaccination with annual OPV campaigns, so-called National Immunization Days (NID) during which all children younger than 5 years received a dose of OPV irrespective of previous immunization history. This principle had been successfully used in Cuba since the early 1960s. By the mid-1980s, the success of these campaigns in Latin American countries was so good that a desire for the global eradication of poliomyelitis emerged.

In 1988, the World Health Assembly accepted the resolution *WHA41.28 Global eradication of poliomyelitis by the year 2000.* The subsequently created program, the Global Polio Eradication Initiative (GPEI), is spearheaded by the WHO, the Centers for Disease Control and Prevention (CDC) of the USA, UNICEF, and Rotary International. More recently, Bill and Melinda Gates Foundation and the GAVI alliance have joined forces with the above organizations.

GPEI includes guidelines for intensified immunization, standards for surveillance, a supporting worldwide laboratory network, and centralized reporting. In addition to routine infant immunizations, NIDs and other

modes of supplementary immunization were recommended to guarantee maximal vaccination coverage. In surveillance, the starting point was a suspected case, a patient with acute flaccid paralysis (AFP). Both local healthcare personnel and ad hoc trained lay "reporters" were supposed to notify these cases to designated epidemiologists who examined the cases, collected stools for virus isolation, and reported the results to a national epidemiological center (NEC). Each country had a nominated national polio laboratory (NPL), which carried out the stool examination and sent possible poliovirus isolates forward to designated polio reference laboratories for further characterization. Both NECs and NPLs reported their results to WHO regional centers, and the latter reported to the WHO Head Quarters (HQ) in Geneva, Switzerland. Before the fight against COVID-19, the global polio eradication initiative was considered the broadest international healthcare action ever performed.

The original target of the GPEI was not reached, but the initial progress was dramatic: starting from an estimated number of 350,000 new cases in 1988, already 10 years of the program reduced the number of annual cases by more than 99% and drastically limited the number of countries with persisting wild poliovirus circulation. Since then, however, various factors (see ► Sect. 8.4.2) have delayed the completion of the desired eradication. Yet, two of the three serotypes of wild poliovirus have been eradicated globally from circulation in humans, type 2 in 1998 and type 3 in 2012. While AFP surveillance remains the gold standard in monitoring the progress of the GPEI, search for virus in feces-contaminated environmental specimens has got an increasingly important supplementary role in monitoring transmission of poliovirus in the target populations. Narrowing genetic divergence of wild polioviruses has finally allowed the use of RT-PCR tests in primary diagnostic procedures. (Previously, genetically closely related nonpolio enteroviruses common throughout the world had confounded direct detection, and the time- and resource-consuming cell culture isolation had to be used.)

The GPEI was so far closest to its target in 2017, with only 22 reported new cases of paralytic disease due to wild poliovirus. Subsequent operational challenges in the two remaining endemic countries, Afghanistan and Pakistan, together with the failure to stop emergence of cVDPV outbreaks by switching trivalent OPV to bivalent OPV (types 1 and 3 only), have increased the annual numbers of new cases to several hundreds again (◘ Fig. 8.3). The ongoing COVID-19 pandemic has interfered with scheduled immunizations against other diseases in several countries. The potential new burden of morbidity due to missed vaccinations is still difficult to predict.

From a European point of view, it is important to note that various factors pose a risk for a putative return of epidemic poliomyelitis to the IPV-immunized world. As mentioned above, the immunity obtained with IPV protects individuals against the paralytic disease, but does not provide the population with a strong herd immunity. Thus, maintaining high-coverage polio immunizations with IPV and national preparedness for preventing further spread of imported poliovirus remain important even after the desired eradication of WPV and cessation of cVDPV transmissions.

8.4.2 Remaining Obstacles of Eradicating Wild Poliovirus Transmission

Wild type 1 poliovirus still persists in human populations in Afghanistan and Pakistan. Failure to eliminate the transmission in these countries in spite of several years of intensive efforts is multifactorial. These factors include limited political power of the respective governments, deteriorated national infrastructure and healthcare systems, and political or religious intrigues reaching as far as to civil wars, intentional disinformation on the goals of GPEI, and repeated hostile attacks toward the vaccinators. Performance of the national immunization programs under these circumstances remains very challenging. The virus is mainly harboring in difficult-to-reach rural populations, but from there, the virus has travelled abroad with asymptomatic humans to countries with shorter or longer polio-free

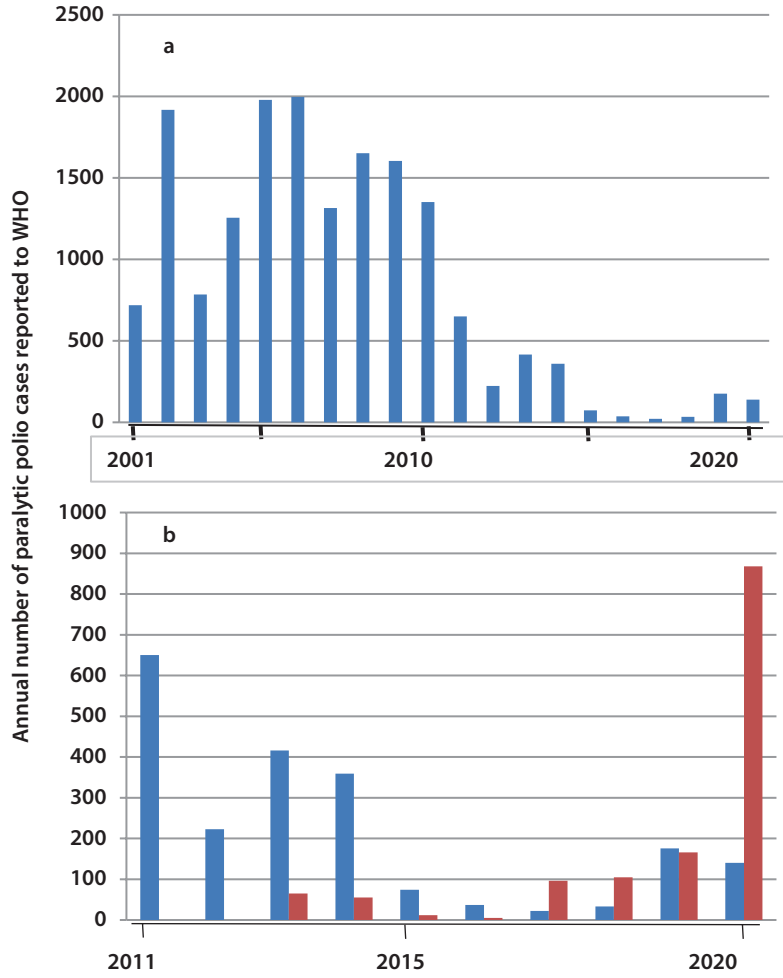


Fig. 8.3 Paralytic cases of poliomyelitis annually reported to WHO. **a** Cases due to wild poliovirus. **b** Cases due to infection by wild PV1 (blue) or cVDPV (red). Twenty out of the cVDPV cases were of type 1, the rest of type 2. (Source of data: ▶ www.polioeradication.org)

history and probably reestablished transmission in susceptible subpopulations and caused cases of paralytic disease. Risk of such events will remain as long as WPV1 is circulating in humans.

8.4.3 Risks of Wild Polioviruses Residing in Known and Unknown Locations

There are plans to replace the old WPV strains in IPV production with the attenuated Sabin strains or with genetically modified avirulent derivatives, but the current IPV manufacturing still uses the original neurovirulent strains. The routine handling of polioviruses and poliovirus-containing specimens in the WHO poliovirus laboratory network and among the vaccine manufacturers follows good laboratory practice, taking into account strict biosecurity principles. However, humans can make mistakes, and for instance, escapes of wild poliovirus from an IPV manufacturing plant to the community or the environment in Europe have been reported.

The WHO "Global Action Plan for Poliovirus Containment" advises member countries to destroy all unnecessary poliovirus stocks and poliovirus-containing speci-

mens. In spite of serious attempts, national surveys may, however, miss historical sets of potentially poliovirus-containing stool specimens collected, for instance, for non-virological research purposes. WHO is aiming at limiting the future poliovirus-handling laboratories, including research laboratories, to a small number of "Poliovirus Essential Facilities," following very strict rules when handling the specimens.

Another type of risk, a theoretical one, is provided by the melting of northern permafrost due to the ongoing global warming. Fortunately, the corresponding latitudes have been sparsely populated for millennia, and there is no direct evidence that polioviruses would be present in the earth of the now melting regions. However, it is known that the permafrost can store infectious viruses for tens of thousands of years, and this possibility should be kept in mind.

8.4.4 Vaccine-Derived Polioviruses

Outbreaks of paralytic disease caused by cVDPV have been stopped by active immunization campaigns initially with trivalent OPV and more recently with the corresponding monovalent OPV. Stocks of monovalent vaccines for all three serotypes are maintained by the WHO. As most of the cVDPV outbreaks have been caused by Sabin 2-derived viruses, a coordinated switch from trivalent to bivalent (1 + 3) OPV took place in OPV-using countries in 2016. Immunity to type 2 poliovirus was designed to be obtained with at least a single dose of trivalent IPV to all neonates. It was also hoped that in this way the emergence of new type 2 cVDPV outbreaks would be prevented. The global process was somewhat hampered by acute shortage of IPV doses, and a few countries had to carry out the switch without the IPV shelter. Unfortunately, the emergence of new type 2 cVDPV outbreaks did not stop but rather significantly increased (◘ Fig. 8.3). Furthermore, it seems that some of the new outbreaks are derived from the monovalent type 2 OPV campaigns carried out to stop an existing circulation of cVDPV. In 2020, paralytic cases due to type cVDPV infection occurred in 19 African countries, Afghanistan, Pakistan, and the Philippines.

So far, cVDPV outbreaks have not spread from the original OPV-immunized population to IPV-using neighboring countries, but this possibility cannot be excluded, especially in the situation of decreasing immunization coverages. It has been proposed that in order to solve the cVDPV problem, live attenuated type 2 poliovirus may have to be returned to routine immunizations, preferably one of the genetically stabilized Sabin 2-derived strains, which have been shown to be immunogenic and safe to use.

Long-term shedding of neurovirulent OPV-derived viruses by rare individuals is yet another risk provided by VDPVs. Stool surveys carried out on immune-deficient (ID) patients known to the healthcare system in several countries suggest that only a small fraction of ID patients presents with persistent shedding of the ID-type vaccine-derived polioviruses (iVDPV). So far, no outbreak caused by iVDPVID-type vaccine-derived polioviruses (iVDPV) has been described, even though the viruses are neurovirulent. On the other hand, several environmental poliovirus isolates share the distinct genetic features of iVDPV. The isolates have been found in different countries in the absence of known poliovirus-shedding ID patients in the region. Thus, not all individuals with a possibly mild ID but enabling persistent poliovirus infection are known to the healthcare systems. Hence, the risk of polio return from long-term iVDPV shedding is difficult to estimate.

8.4.5 OPV and COVID-19

Recently the indirect benefits of several live vaccines, such as BCG and MMR, have drawn attention because of their potential ameliorating effect on clinical course of COVID-19 infection. OPV has also been brought up in this context.

Russian studies in the 1960s and 1970s showed that OPV significantly reduced morbidity from influenza. A randomized controlled trial in Guinea-Bissau showed that

neonatal OPV immunization reduced infant mortality. A small study in Finland suggested that OPV, in comparison with IPV, reduced the occurrence of otitis media in infants.

The positive effects of OPV, like those of BCG and MMR, on unrelated infections may be explained by stimulation or "training" of innate immunity. While there is no direct proof of OPV's effect on COVID-19, such an effect appears plausible.

Further Reading

Chumakov MP, Voroshilova MK, Drozdov SG, et al. Some results of the work on mass immunization in the Soviet Union with live poliovirus vaccine prepared from Sabin strains. Bull World Health Organ. 1961;25:79–91.

Enders JF, Weller TH, Robbins FC. Cultivation of the Lansing strain of poliomyelitis virus in cultures of various human embryonic tissues. Science. 1949;109:85–7.

Heymann D, Ahmed Q. The polio eradication end game: what it means for Europe. Euro Surveill. 2014;19:20702.

Kalkowska DA, Pallansh MA, Wilkinson A, et al. Updated characterization of outbreak response strategies for 2019-2029: Impacts of using novel type 2 oral poliovirus vaccine strain. Risk Anal. 2020; https://doi.org/10.1111/risa.13622.

Minor P. Vaccine-derived poliovirus (VDPV): impact on poliomyelitis eradication. Vaccine. 2009;27:2649–52.

Sabin AB. Oral poliovirus vaccine: history of its development and use and current challenge to eliminate poliomyelitis from the world. J Infect Dis. 1985;151:420–36.

Salk JE. Poliomyelitis vaccine in the fall of 1955. Am J Public Health Nations Health. 1956;46:1–14.

Salk D, van Wezel AL, Salk J. Induction of long-term immunity to paralytic poliomyelitis by use of non-infectious vaccine. Lancet. 1984;2:1317–21.

Thomassen YE, et al. Next generation inactivated polio vaccine manufacturing to support post polio-eradication biosafety goals. PLoS One. 2013;8(12):e83374.

Van Damme P, De Coster I, Bandyopadhyay AS, et al. The safety and immunogenicity of two novel live attenuated monovalent (serotype 2) oral poliovirus vaccines in healthy adults: a double-blind, single-centre phase 1 study. Lancet. 2019;394:148−158.

Web Link

http://www.polioeradication.org.

Measles–Mumps–Rubella Vaccine

Timo Vesikari and Vytautas Usonis

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_9

9.1 Measles and Measles Vaccine

Measles is a systemic viral infection transmitted via airborne droplets and characterized by respiratory symptoms and rash. Common complications are pneumonia, otitis, and diarrhea. Measles is sometimes regarded as an ordinary childhood disease that children should preferably experience to "strengthen" their immune system. However, it is important to remember that measles is a serious and potentially fatal disease, with 2–8% mortality in developing countries. Historically, measles carried a significant risk for mortality in Europe as well; even in the recent outbreaks of measles in Europe, there have been fatalities.

The development of a vaccine against measles became possible after isolation of the measles virus by Enders and Peebles in 1954. A nonlive measles vaccine was developed and used for a few years in the USA in the 1960s. The vaccine was withdrawn because some vaccinated children upon exposure to measles developed atypical and severe forms of measles.

Isolation of the measles virus paved the way to attenuation and live vaccine development. The first vaccine strain was called Edmonston after the boy from whom the virus was isolated. Most measles vaccines in the world and all those in Europe are derived from the Edmonston isolate. The two currently available vaccine strains, Schwarz (Edmonston A) and Moraten (Edmonston B), represent two different cell culture passage branches of the original, but are at practically the same attenuation level. Several studies have addressed possible differences in the immunogenicity and safety profile of these vaccines. The level of attenuation of the measles vaccine is a carefully chosen balance between sufficient immunogenicity and minimal (although still substantial) reactogenicity.

A less attenuated version of Edmonston B strain, Edmonston–Zagreb (E–Z), was developed and used in the former Yugoslavia. The E–Z strain was cultured in WI-38 human fibroblast cells. The vaccine was regarded as a more potent (than the current one) measles vaccine that could be given at the age 4–6 months in the presence of maternal antibody, thereby contributing to measles elimination efforts in developing countries. However, it was found that this measles vaccine, initially endorsed by the WHO, was associated with increased all-cause mortality in girls, and the approach was withdrawn. Subsequently, widespread use of the present measles vaccines has shown that a more potent vaccine is not needed, but measles can be eliminated with the currently available vaccines if used extensively.

A Russian measles vaccine, Leningrad 16 strain, which was not derived from Edmonston, was given on a large scale in Eastern European countries over many decades. Therefore, measles immunity in adults in those countries is reliant on vaccination with Leningrad 16, which is no longer used in Europe.

In the 1970s, when measles vaccination was being introduced into Europe, mortality from measles was already low. Major arguments for the introduction of vaccine included the prevention of complications, notably meningoencephalitis, which occurs at a rate of 1:1000–1:2000 and may leave permanent sequelae. Another measles-related problem is subacute sclerosing panencephalitis (SSPE), which occurs several years after measles at an early age at a rate of 1:100,000 and is invariably fatal; preventing SSPE is an important goal of measles vaccination. Less serious complications such as pneumonia and otitis media are very common after measles. All the complications combined make an argument in favor of measles vaccination in Europe.

Still, these arguments regarding measles vaccination were not compelling enough at that time to convince all physicians and other healthcare workers, and the coverage of single measles vaccination until the introduction of MMR vaccination programs remained at 60–70% in many Western European countries. This level of immunization reduced the epidemics, but postponed the acquisition of measles to adolescent age, resulting in many cases of serious disease and even deaths in young people. In contrast, in many Eastern European countries with mandatory measles vaccination programs, measles was virtually

eliminated. In Western European countries, the elimination of measles only started with the introduction of two-dose programs of MMR vaccine.

As measles is targeted for eradication by the WHO, Europe will have to do its share in the process, which adds another compelling reason for measles immunization. Globally, measles-associated deaths have decreased from about 1.5 million a year to 134,200 in 2015, owing to vaccinations. As measles is highly infectious, over 95% vaccine coverage is needed for control, and only a very high global coverage can result in eradication. Elimination of indigenous measles in Latin America is a strong indication that it can be done, and Europe should be able to accomplish the same. The WHO strategic plan is to eliminate measles in at least five WHO regions.

Cases of measles and rubella continue to occur sporadically and in outbreaks in European countries (Fig. 9.1). In 2019, there were 13,200 reports of measles to the European Centre for Disease Prevention and Control, of which 10,561 (80%) were laboratory confirmed. The remaining 2639 cases were reported as "probable" (10%), "possible" (10%), and "unknown" (<1%). The overall notification rate in 2019 was 25.4 cases per 1,000,000 population ranged from 1 case per 1,000,000 population in Portugal to 298.5 in Lithuania. The true number was probably even higher.

9.2 Mumps and Mumps Vaccine

Mumps is a generalized viral infection transmitted via airborne droplets or direct contact with infected saliva. Transmission depends on the close contact and increases in overcrowded conditions. The classical manifestation is the swelling of one or both parotid glands. Other manifestations of mumps may be viral meningitis, encephalitis, pancreatitis, mastitis, orchitis, and arthropa-

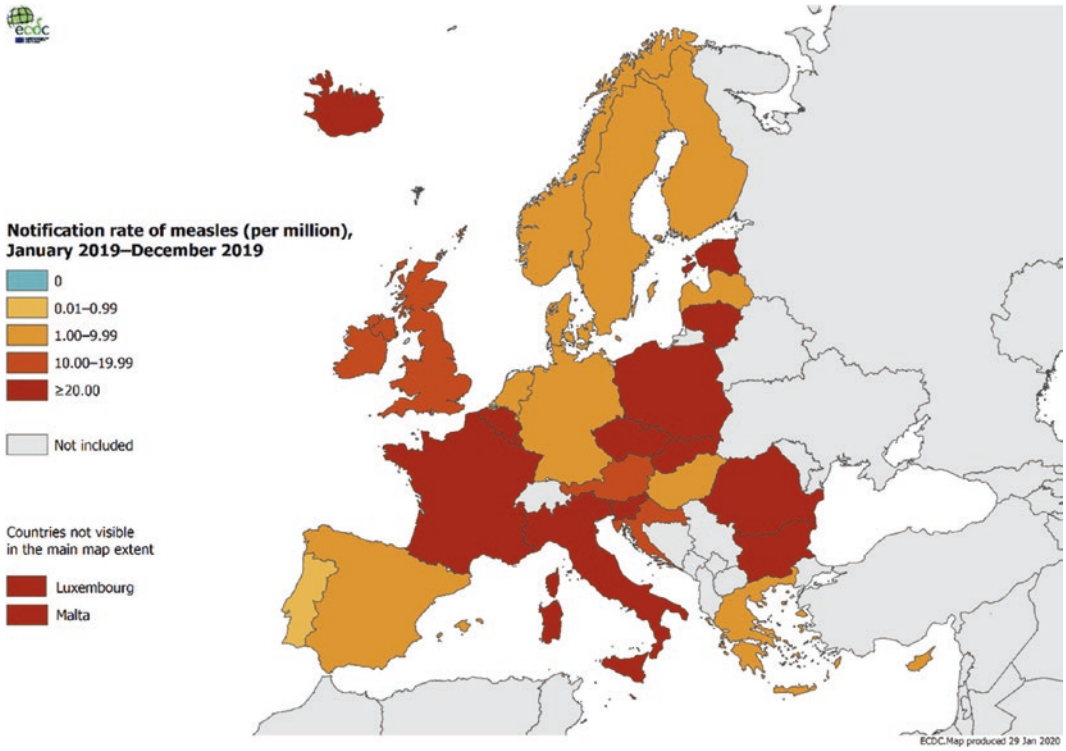


Fig. 9.1 Distribution of measles cases per 1,000,000 population by country, EU/EEA, 2019. (*Source*: ▶ https://www.ecdc.europa.eu/sites/default/files/documents/measles-2019-aer.pdf)

thy. Orchitis in post-pubertal males may result in sterility.

The case for mumps vaccination is less compelling than for measles and rubella, but still strong enough to justify the inclusion of the mumps component in the MMR vaccine. Since the introduction of vaccination, the incidence of mumps has decreased dramatically. In pre-vaccine era, mumps was characterized by 4- to 5-year epidemic cycles. Natural mumps infection is thought to confer lifelong protection. Mumps is typically a mild childhood disease that begins with non-specific symptoms followed by a unilateral or bilateral swelling of the parotid glands. Meninges, pancreas, and testes are other targets. An illustrative example of the clinical course and significance of mumps comes from a naïve population on St. Lawrence Island where an epidemic of mumps resulted in clinical disease in 65% and subclinical infection in 35%; of those with clinical mumps, 11% had meningitis and 25% of post-pubertal men had orchitis. Prevention of such complications is the reason for mumps vaccination.

In the past, inactivated mumps vaccines were developed and used in targeted populations such as the military in Finland. The protection conferred by the inactivated mumps vaccine against orchitis was good, but not as durable as that induced by a live mumps vaccine. In contrast to measles, no atypical forms of mumps have been reported in the recipients of a killed vaccine.

A live attenuated mumps vaccine was developed by the serial passaging in chicken embryo of fibroblast cells. The vaccine strain is called Jeryl Lynn, according to the patient from whom the virus was isolated; the developer was Maurice Hilleman at Merck Research Laboratories. Only this one mumps vaccine strain survives in the current major MMR vaccines. The Jeryl Lynn strain barely causes any adverse reactions. However, the single mumps vaccine is no longer available. Present strategies to control mumps are closely integrated with existing goals of measles and rubella control or elimination, and the MMR vaccine is used as a common tool.

A Japanese mumps vaccine strain Urabe AM9 was incorporated in an early version of GSK's MMR vaccine, but was withdrawn as it was found to cause meningitis at a rate of 1 in 50,000 recipients. Afterward, GSK re-isolated a mumps vaccine virus from the Jeryl Lynn vaccine preparation, by choosing only one plaque variant of the two present in the original Jeryl Lynn. The isolate was called RIT4385 and is now incorporated in GSK's MMR vaccine. Comparative studies of the RIT 4385 and Jeryl Lynn vaccines showed a high safety level and similar seroconversion rates.

The Leningrad-3 mumps vaccine strain was developed in the former Soviet Union. This strain was further attenuated in Croatia, named Leningrad–Zagreb, and used for vaccine production in Croatia and India. The Rubini strain was first licensed in Switzerland in 1985. However, substantially lower rates of seroconversion and effectiveness among recipients of Rubini strain vaccine compared with those vaccinated with Jeryl Lynn or Urabe Am9 strains were observed. Therefore, the WHO recommends that the Rubini strain vaccine should not be used in national immunization programs.

9.3 Rubella and Rubella Vaccine

Rubella is a systemic viral infection that is highly contagious. In children, rubella is characterized by a mild fever and a short-living rash. Rubella is a mild disease and may be unrecognized or misdiagnosed in young children. Furthermore, up to 50% of rubella infections may be subclinical. These cases are still contagious in contact with unvaccinated and non-immune pregnant women. If a non-immune pregnant woman gets infected, the rubella virus may be transmitted to the fetus and induce serious birth defects described as congenital rubella syndrome (CRS).

The association of rubella in early pregnancy with congenital cataract in the infant was described by Norman Gregg in Australia in 1941, but it was not until 1964 and a major epidemic of rubella in the USA that resulted in an estimated 20,000 babies with damage that the disease was fully appreciated and vaccine development started. The rubella virus had been isolated

just 2 years earlier independently by Weller and Neva and by Parkman and co-workers in the USA. The case for rubella vaccination lies primarily in the prevention of CRS. Systematic vaccination against rubella, usually in combination with measles, has eliminated both the congenital and acquired infections from some industrialized countries and Latin America.

Although CRS is very rare today, it should be kept in mind as a motivation for vaccination. CRS is limited to cases of maternal rubella in the first trimester of pregnancy, although cases of hearing loss may occur up to 16 weeks of pregnancy. In the first ≤11 weeks of pregnancy, the rubella virus crosses the placenta in 90% of cases and results in clinical sequelae in almost all, even though the severity of CRS varies. The classical triad is heart–eye–ear. Cardiovascular anomalies typically include pulmonary stenosis and patent ductus arteriosus. Ocular manifestations include retinopathy, cataract, and glaucoma and may result in blindness. Hearing loss is the most common single manifestation of CRS and may be bilateral or unilateral. In addition to isolated organ damage, the full-blown CRS includes generalized infection of the newborn, with enlarged liver and spleen, purpura, jaundice, and CNS involvement. After mid-pregnancy, the rubella virus may still be transmitted to the fetus in about 50% of the cases, but does not cause any clinical damage.

Several live attenuated rubella vaccines were developed and licensed after isolation of the rubella virus in the 1960s. Early licensed vaccines included the Cendehill strain grown in rabbit kidney cells and the HPV77 strain isolated in monkey kidney cells and grown in duck embryo fibroblasts. RA27/3 was discovered in 1969 and is the only strain that survives today, as all previously registered vaccines were less immunogenic and more reactogenic than RA27/3.

The RA27/3 strain was isolated from a rubella-related abortion, and the virus was attenuated in WI38 human fibroblast cells. Therefore, the passage history is entirely "human." RA27/3 is highly immunogenic and nearly a 100% seroconversion rate is reached with a single rubella vaccination or in the MMR combination. Adverse effects attributable to the rubella component in MMR vaccination in children are rare. A notable adverse event is thrombocytopenia, which may manifest in about 1:50,000 vaccine recipients. In adult vaccinees, the rubella vaccine may be associated with joint pain or even arthritis; however, these were much more common in association with the early rubella vaccines than with RA27/3.

Currently, the only existing strategy to prevent CRS is the elimination of rubella by vaccination of all infants and children with the MMR vaccine. Previously, the single rubella vaccine was used for targeted vaccination of women and girls. The target groups included women postpartum (after the birth of the first child) or pre-pubertal girls. Neither strategy ever reached a high coverage, and both were ineffective in the prevention of CRS. Moreover, an inadequate level of rubella immunization of adolescent girls increases the number of sero-susceptible women at childbearing age and enhances the risk of rubella in pregnancy. For example, CRS increased in Greece and Romania after outbreaks of rubella. Rubella is targeted for elimination in Europe, but continues to occur in many European countries. Decreasing of the coverage of vaccination with the MMR vaccine due to antivaccine activities or due to Covid-19-related limitations may pose risk of resurgence of rubella and CRS.

9.4 Measles–Rubella Vaccine

Measles and rubella are targeted for global elimination/eradication, whereas mumps is not. Not all countries consider mumps a priority for vaccination and prefer to use the measles–rubella (MR) vaccine instead. Globally, an Indian-made MR vaccine is being used extensively (150 million doses distributed), but is not available in Europe.

9.5 Measles–Mumps–Rubella Vaccine

Live attenuated measles, mumps, and rubella vaccines were combined into the MMR vaccine. Merck's MMR vaccine was first introduced in the USA in 1971, and the composition was changed to the current one in 1978 (MMRII®). The MMRII® vaccine contains the Moraten strain of the measles vaccine, the Jeryl Lynn strain of the mumps vaccine, and the RA27/3 strain of the rubella vaccine. In Europe, the same vaccine has been marketed as MMR VaxPro® (SP-MSD). The first licensed MMR vaccine contained the HPV77/DE5 strain of the rubella vaccine, but this was replaced in 1978 by RA27/3 to make the MMRII® vaccine.

Although MMR vaccinations were started in Europe later than in the USA, the practice of giving two doses of MMR was initiated in Sweden and Finland in 1982. The introduction of the two-dose MMR vaccination programs offered a new tool for the elimination of measles in Europe. The two-dose program was purely empirical, but had the following rationale:

1. Filling the immunogenicity gap in those who may remain susceptible after the first dose.
2. A booster effect in a proportion of the children who have taken the first dose.
3. Single-dose MMR vaccination policy inevitably misses a certain proportion of infants and a second dose catches those individuals who have not received their primary MMR dose.

Subsequently, it was realized that an important mechanism by which a second dose of MMR vaccine enhances protection (at least against measles) is the increased avidity of IgG antibodies. In Sweden, the second dose of MMR was given at the age of 12 years with the idea of maximizing protection against mumps and rubella just before puberty; this practice remains in some countries (Fig. 9.2). In Finland, the second dose is given at 6 years of age. At present, the timing of the second dose varies greatly from country to country (Fig. 9.2). With the two-dose program, Finland became the first country to eliminate indigenous measles, mumps, and rubella by 1994. To reach this target, the coverage had to be over 95% for the two doses.

In some countries with a lower coverage, but with the intention of eliminating measles, a much shorter interval between the two doses of MMR vaccine is being recommended. The practice of giving the doses of MMR at a short, even only 3-month interval was started in Germany and has spread to other European countries. Currently, there are a multitude of MMR vaccination schedules in Europe (Fig. 9.2). The "short" interval schedules are specifically targeted at the elimination of measles, whereas the "long" interval schedules target boosting the immunity for durable protection into adolescence and beyond. There is no longer any justification for a single-dose policy.

The MMR vaccine manufactured by GSK originally contained the Urabe AM9 strain of the mumps vaccine and was withdrawn in 1986. GSK replaced the mumps component with a one-plaque variant of the Jeryl Lynn strain called RIT 4385. Thus, the present vaccine, Priorix®, contains the Schwarz strain of measles, the RIT 4385 strain of mumps, and the RA27/3 strain of rubella. Although the measles component is comparable with and the rubella component the same as in MMR-II, the mumps component was initially less immunogenic. However, with dose adjustments, the immunogenicity of RIT 4385 has been improved, and in general, the two vaccines are quite similar with regard to immunogenicity. In European countries, the two MMR vaccines may be used interchangeably. Both vaccines are safe and effective for the prevention of measles, mumps, and rubella/CRS.

Numerous clinical studies performed before the registration demonstrated the safety of currently used MMR vaccines. This safety is also confirmed in post-marketing surveillance. The most significant adverse reaction following MMR administration is fever. The timing of the fever is characteristic and occurs 7–10 days after vaccination (Fig. 9.3). A rash may appear during the

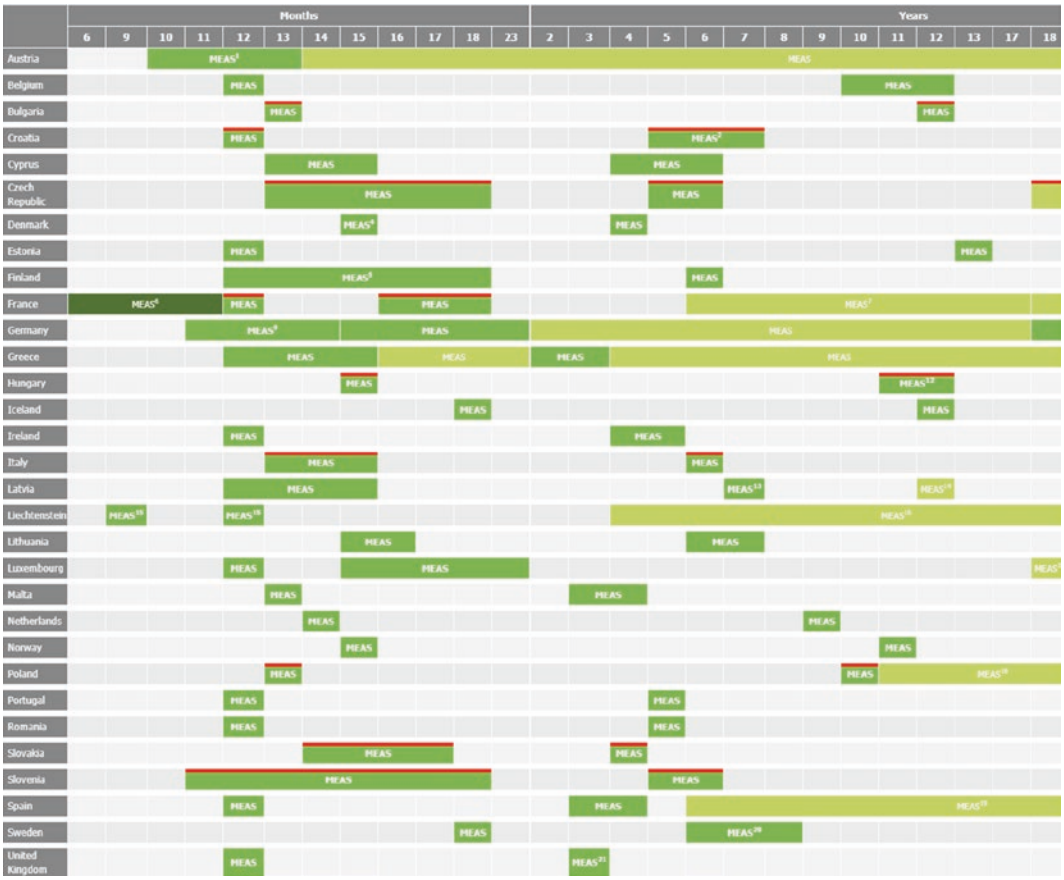


Fig. 9.2 Measles–mumps–rubella vaccination schedules in Europe. Red color – mandatory vaccination. European Centre for Disease Prevention and Control (ECDC) ▶ http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx

second week after vaccination, but other adverse events are very rare. No cases of viral meningitis have been reported after MMR vaccines currently used in Europe.

In 1998, Wakefield et al. published a paper in *The Lancet* reporting that MMR vaccination, but not the single measles vaccine, was associated with autism. The paper was later retracted by *The Lancet*. Still, the so-called Wakefield hypothesis endured. In 2001, a review by the Institute of Medicine (USA) concluded that the evidence rejected a causal relationship at the population level between the MMR vaccine and autistic spectrum disorder (ASD). The hypothesis has been tested in a number of observational and epidemiological studies, and the main conclusion of the studies is that the MMR vaccination is not associated with an increased risk of ASDs.

9.6 MMR Vaccination of Special Groups

In exceptional cases, the MMR vaccine can be given to 6- to 9-month-old infants if they are at a high risk of becoming infected, e.g., during a measles outbreak or travel. These children may not respond to this early dose because of residual maternal antibodies; therefore, they need the two standard MMR doses, first at 12–13 months of age and a second dose later.

The MMR vaccine is recommended to nonpregnant women of childbearing age if they have no proof of immunity against rubella or if this information is not available. It cannot be given to pregnant women, but it can be given after delivery. However, in cases of inadvertent vaccination during pregnancy,

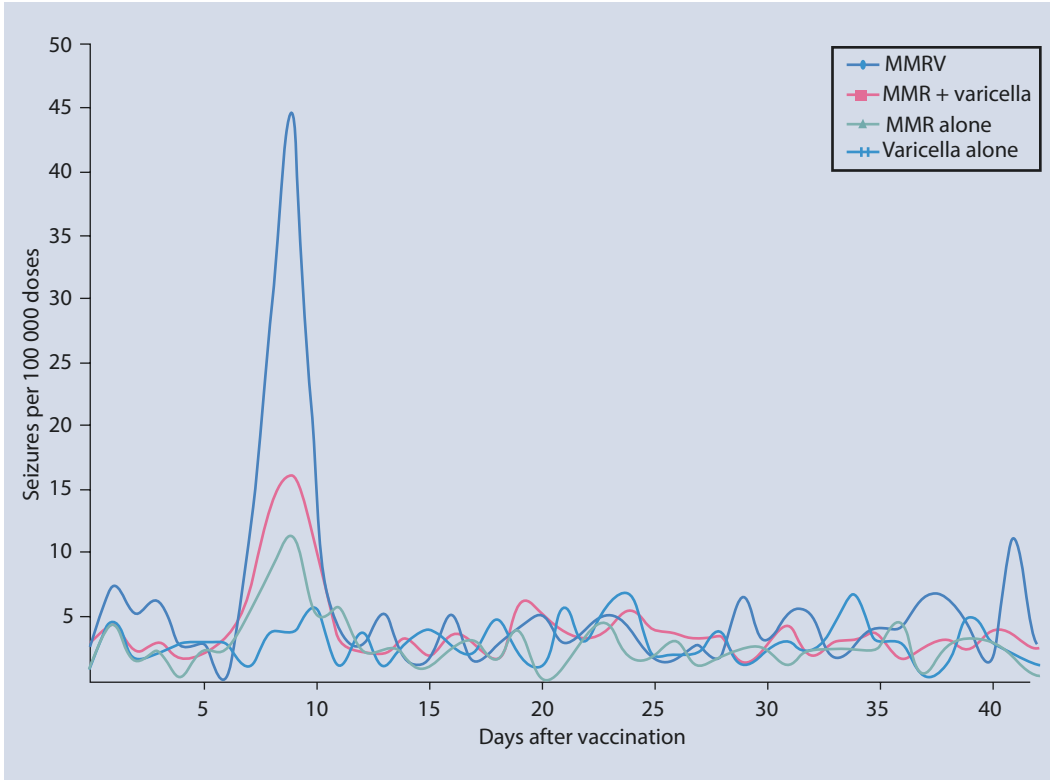


Fig. 9.3 Measles–mumps–rubella–varicella combination vaccine and the risk of febrile seizures. (Reproduced with permission Klein et al. 2010)

there is no need to take any measures, as transmission of the rubella vaccine virus to the fetus is rare and is not known to cause clinical harm to the fetus.

If vaccination against measles, mumps, or rubella is needed outside the current childhood immunization programs, the MMR vaccine should be given, rather than any of the single components. There is no harm in administering "extra" doses of MMR to previously immunized persons. In any case, single measles, mumps, or rubella vaccines are no longer available in Europe.

The MMR vaccine cannot be given to persons who have had an anaphylactic reaction to a previous dose of the MMR vaccine or a component of it. MMR is a live virus vaccine, and it should not be given to persons with an impaired immune response, e.g., those treated with high-dose steroids, those treated for cancer with chemotherapy or radiotherapy, or those who are on immunosuppressive drugs after an organ transplant.

9.7 Measles–Mumps–Rubella–Varicella Vaccine

The measles–mumps–rubella (MMR)-varicella (MMRV) vaccine is also described in Chap. ▶ 10. The main rationale of a combined MMRV vaccine is obviously the easier administration, with one injection only, of both MMR and varicella vaccines. Although the development of a combined MMRV vaccine began in the 1980s, it took almost two decades to get the vaccine licensed. The reason was twofold: (1) if a standard dose of varicella vaccine was combined with measles–mumps–rubella–varicella (MMRV) vaccine, it was not sufficiently immunogenic, and (2) if the titer of the varicella component was increased for sufficient immunogenicity, it also increased the reactogenicity of the combination in comparison with MMR. The current licensed MMRV vaccines represent a compromise and balance between these two issues.

The immunogenicity of MMRV for varicella zoster virus is clearly higher than that of a single varicella vaccine (▶ Table 10.2). The immunogenicity for measles, mumps, and rubella may also be slightly higher, but the difference is not critical and not an argument in favor of the use of MMRV instead of MMR. Altogether, for the sake of the elimination of measles and rubella and for the control of mumps, there is no reason to use MMRV instead of MMR vaccine. Rather, MMRV should be seen as a tool for varicella vaccination in countries that have achieved good control of the MMR diseases.

The reactogenicity of the MMRV vaccine after primary vaccination has become a significant issue (◘ Fig. 9.3). The fever rate is more than double that of MMR (and varicella given separately in a different arm at the same time), and the risk of febrile convulsions increases in the same proportion.

After the licensure of the MMRV vaccine in 2006, the ACIP in the USA recommended that it be the choice for varicella vaccination. However, because of the issue of febrile convulsions, the recommendation was changed to no-recommendation, i.e., the physician could choose between MMRV and separate MMR and varicella vaccination. In practice, the separate administration of MMR and varicella vaccines has become more common for primary vaccination, whereas for the second dose, MMRV is often chosen for convenience. Fever and febrile convulsions are not an issue for the booster vaccination, no matter how long the interval is between the first and second doses.

In Europe, febrile convulsions are not regarded as the same kind of problem as in the USA, and MMRV is given for the primary vaccination in parts of Italy (Lombardy, Sicily) that have implemented varicella vaccination and in Germany and Greece. In any case, febrile reactions can be anticipated because of the well-known timing, and anti-febrile medication can be initiated to prevent seizures.

Two licensed MMRV vaccines are available in Europe: Priorix-Tetra® (GSK) and Pro-Quad (Merck). The descriptions of the vaccines are shown in ◘ Table 9.1.

◘ **Table 9.1** Descriptions of vaccines

Component	Priorix-Tetra	ProQuad
Measles	Schwarz strain	Enders' Edmonston
Mumps	RIT 4385 strain, derived from Jeryl Lynn strain	Jeryl Lynn™ (Level B)
Rubella	Wistar RA 27/3 strain	Wistar RA 27/3 strain
Varicella	Oka strain	Oka/Merck strain

9.8 MMR Vaccine and Covid-19

MMR vaccine is believed to prevent or ameliorate Covid-19 disease in two ways. MMR vaccine can broadly boost immunity and have a "non-specific" beneficial effect on the course of Covid-19 infection. Secondly, the measles and rubella components of the vaccine share up to 30 sequences with SARS-CoV-2 S-protein. In measles virus the similarity is found on the fusion (glyco)protein and in rubella on virus envelope glycoprotein E1.

Widely used MMR vaccination could explain why children generally have a mild or subclinical course of Covid-19 infection. Furthermore, Covid-19 infection was observed to run a mild course among US Navy recruits who had recently received a booster dose of MMR vaccine.

MMR vaccine has been dubbed as "a low risk – high reward" preventive measure against Covid-19. In any case even the uncontrolled re-emphasize the importance of a full – two dose immunization with MMR vaccine. An extra dose may be well worth considering.

Meanwhile, a controlled trial including 30,000 health care workers in several countries is underway to find out if there is a beneficial effect of MMR vaccine against Covid-19 in adults.

9.9 Measles-Based Covid-19 Vaccine

In the midst of finding new approaches for development of Covid-19 vaccines, also measles virus has been used as a vector for coronavirus antigens. This platform was previously used to develop vaccines both for SARS and MERS. These vector vaccines contained recombinant measles virus expressing the S protein of SARS and MERS, respectively. The vaccines elicited both neutralizing antibodies and T-cells producing interferon gamma.

In the new approach, the gene that encodes the SARS-CoV-2 protein was inserted into two distinct parts of the measles virus. The incorporation of the S protein in measles virus caused a decrease in multiplication but increase in fusion activity.

The recombinant measles-SARS-CoV-2 S protein vaccine induces neutralizing antibodies both to measles and Covid-19 viruses. The immune response is of Th1 type, with IgG2 antibody and T-helper predominance summed up as a broad and robust SARS-CoV-2-specific immune response.

The recombinant vaccine can be produced following the process of routine measles vaccine production. With the speed of coronavirus vaccine development overall, this candidate vaccine may soon enter efficacy trials. Even if successful, the recombinant vaccine would not substitute standard measles vaccine although it might induce a booster in measles antibodies.

Further Reading

Bolotovski V, et al. Immunization of 6 and 9 month old infants with AIK-C, Edmonston-Zagreb, Leningrad-16 and Schwarz strains of measles vaccine. Int J Epidemiol. 1994;23(5):1069–77.

Bottiger M, et al. Swedish experience of two dose vaccination programme aiming at eliminating measles, mumps and rubella. BMJ. 1987;295:1264–7.

Davis NF, et al. The increasing incidence of mumps orchitis: a comprehensive review. BJU Int. 2010;105(8):1060–5.

Edmunds WJ, et al. The pre-vaccination epidemiology of measles, mumps and rubella in Europe: implications for modelling studies. Epidemiol Infect. 2000;125(3):635–50.

Enders J. Measles virus. Historical review, isolation, and behavior in various systems. Am J Dis Child. 1962;103:282–7.

Enders JF, Peebles TC. Propagation in tissue cultures of cytopathic agents from patients with measles. Proc Soc Exp Biol Med. 1954;86:277–86.

Fidel PL, Noverr MC. Could an Unrelated Live Attenuated Vaccine Serve as a Preventive Measure To Dampen Septic Inflammation Associated with COVID-19 Infection? Bio 2020;11e.00907-20.

Garenne M, et al. Child mortality after high-titre measles vaccines: prospective study in Senegal. Lancet. 1991;338(8772):903–7.

Hörner C et al. A Highly Immunogenic Measles Virus-based Th1-biased COVID-19 Vaccine. bioRxiv preprint. https://doi.org/10.1101/2020.07.11.198291.

Ikić DM. Edmonston-Zagreb strain of measles vaccine: epidemiologic evaluation in Yugoslavia. Rev Infect Dis. 1983;5(3):558– 63.

Immunization Safety Review Committee, Immunization safety review. Vaccines and autism. 2004, Washington, DC: National Academies Press. p. 214.

Klein N, Fireman B, Yih K, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics 2010;126(1):e1–8.

Lievano F, et al. Measles, mumps, and rubella virus vaccine (M–M–R™II): a review of 32 years of clinical and postmarketing experience. Vaccine. 2012;30(48):6918–26.

Mercader S, Garcia P, Bellini WJ. Measles virus IgG avidity assay for use in classification of measles vaccine failure in measles elimination settings. Clin Vaccine Immunol 2012;19:1810–1817.

Peltola H, et al. The elimination of indigenous measles, mumps, and rubella from Finland by a 12-year, two-dose vaccination program. N Engl J Med. 1994;331(21):1397–402.

Peltola H, et al. Measles, mumps, and rubella in Finland: 25 years of a nationwide elimination programme. Lancet Infect Dis. 2008;8:796–803.

Plotkin SA. The history of rubella and rubella vaccination leading to elimination. Clin Infect Dis. 2006;43(Suppl 3):S164–8.

Plotkin S, Mortimer E. Vaccines. second ed. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo: W.B. Saunders Company; 1994.

Plotkin SA, et al. Attenuation of RA27/3 rubella virus in WI-38 human diploid cells. Am J Dis Child. 1969;118:178–85.

Sidiq KR, Sabir DK, Shakhawan MA, Kodzius R. Does Early Childhood Vaccination Protect Against COVID-19? Front Mol Biosci 2020;7:120.

Stratton K, et al. Measles-mumps-rubella vaccine and autism. Immunization Safety Review. National Academy Press, Washington, DC; 2001.

Usonis V, et al. Comparative study of reactogenicity and immunogenicity of new and established measles, mumps and rubella vaccines in healthy children. Infection. 1998;26(4):222–6.

Usonis V, et al. Reactogenicity and immunogenicity of a new live attenuated combined measles, mumps and rubella vaccine in healthy children. Pediatr Infect Dis J. 1999;18(1):42–8.

Vesikari T, Sadzot-Delvaux C, Rentier B, Gershon A. Increasing coverage and efficiency of measles, mumps, and rubella vaccine and introducing universal varicella vaccination in Europe: a role for the combined vaccine. Pediatr Infect Dis J. 2007;26(7):632–8.

Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet 1998;351:637–41.

WHO Euro. Measles and rubella elimination. Package for accelerated action 2013–2015.

WHO Position Paper. Mumps virus vaccines. Wkly Epidemiol Rec. 2007;82(7):51–60.

Varicella Vaccines

Vana Spoulou, Johannes Liese, and Timo Vesikari

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_10

10.1 Burden of Varicella Disease

Primary varicella zoster virus (VZV) infection, or chickenpox, is characterized by generalized pruritic rash, which rapidly progresses from macular to papular and finally vesicular before crusting. In an unvaccinated population it affects almost all persons and usually manifests between 1 and 9 years of age.

Varicella usually occurs in healthy children as an uncomplicated disease. However, severe disease may occur, especially among adolescents, adults, pregnant women, and the immunocompromised patients but also in children without underlying disease. About one half of the severe cases are in subjects without any known risk factor.

Severe bacterial skin infection is a common complication of varicella. CNS manifestations include febrile or cerebral convulsions, cerebellar ataxia, encephalitis, Guillain–Barré syndrome, facial palsy, and cerebral vasculitis. Other frequent viral complications are pneumonia, hepatitis, thrombocytopenia, nephrotic syndrome, and pancreatitis. Severe complications including bacteremia and toxic shock syndrome, Reye syndrome (encephalopathy and hepatic failure following aspirin treatment in children with varicella), and necrotizing fasciitis, purpura fulminans, and disseminated coagulopathy are rare, but associated with significant mortality. Neonatal varicella, occurring in newborns between the fifth and the 12th day of life, is associated with mortality in up to 20% of cases. Congenital VZV infection resulting from varicella in the first 26 weeks of pregnancy causes severe abnormalities of the skin, CNS, eyes, and other organs in the fetus.

Prevention of severe varicella and its complications is a major goal of varicella vaccination. The two main reasons why varicella vaccination should be targeted at all healthy children are (1) severe and complicated cases of varicella may occur in persons without risk factors and (2) children with risk factors such as primary or secondary immunodeficiency (due to, e.g., cancer or corticosteroid therapy) should not be vaccinated with a live attenuated varicella vaccine and therefore can only be protected by herd protection resulting from high vaccine coverage in the healthy population.

10.2 VZV Epidemiology

Varicella zoster virus (VZV) is transmitted by respiratory secretions or vesicle fluid. The incubation period is usually 14–16 days, with a range of 10–21 days. Transmission from person to person may occur from 1–2 days before the onset of the rash until the fifth day after the onset of the rash, or until all lesions have crusted.

In the absence of vaccination, the annual number of varicella cases in Europe is close to the country's birth cohort, and nearly 95% of the population will have been infected by VZV by the age of 10 years. In the USA before the introduction of general varicella vaccination, most cases occurred in children aged 5–9 years, whereas in central and northern European countries, the age group of 1–4 years was (and is) mainly affected (Fig. 10.1a). The highest hospitalization rates are reported among those under 1 year of age followed by immunocompromised subjects and pregnant women. Before varicella vaccinations, there were about 100 deaths from varicella in the USA and 4–10 deaths in Germany each year.

Following primary infection, the virus establishes latency in the sensory nerve ganglia and can reactivate when natural immunity wanes, leading to herpes zoster (HZ). The risk of HZ increases with age starting from about 50 years of age (Fig. 10.1b). One third of HZ patients over 70 develop postherpetic neuralgia (PHN), which may be refractory to various treatments, such as antivirals, nonsteroidal anti-inflammatory agents, corticosteroids, and tricyclic antidepressants. This is a major argument in favor of the development and use of vaccines against HZ.

10.3 Varicella Vaccines

Live attenuated varicella vaccine was developed by Takahashi in 1974. The viral strain that has been used as a vaccine was isolated from a Japanese child with varicella, named Oka, and was then attenuated through sequential passages in tissue cultures and at a low temperature. The "Oka" strain is currently used for the production of all licensed varicella vaccines worldwide.

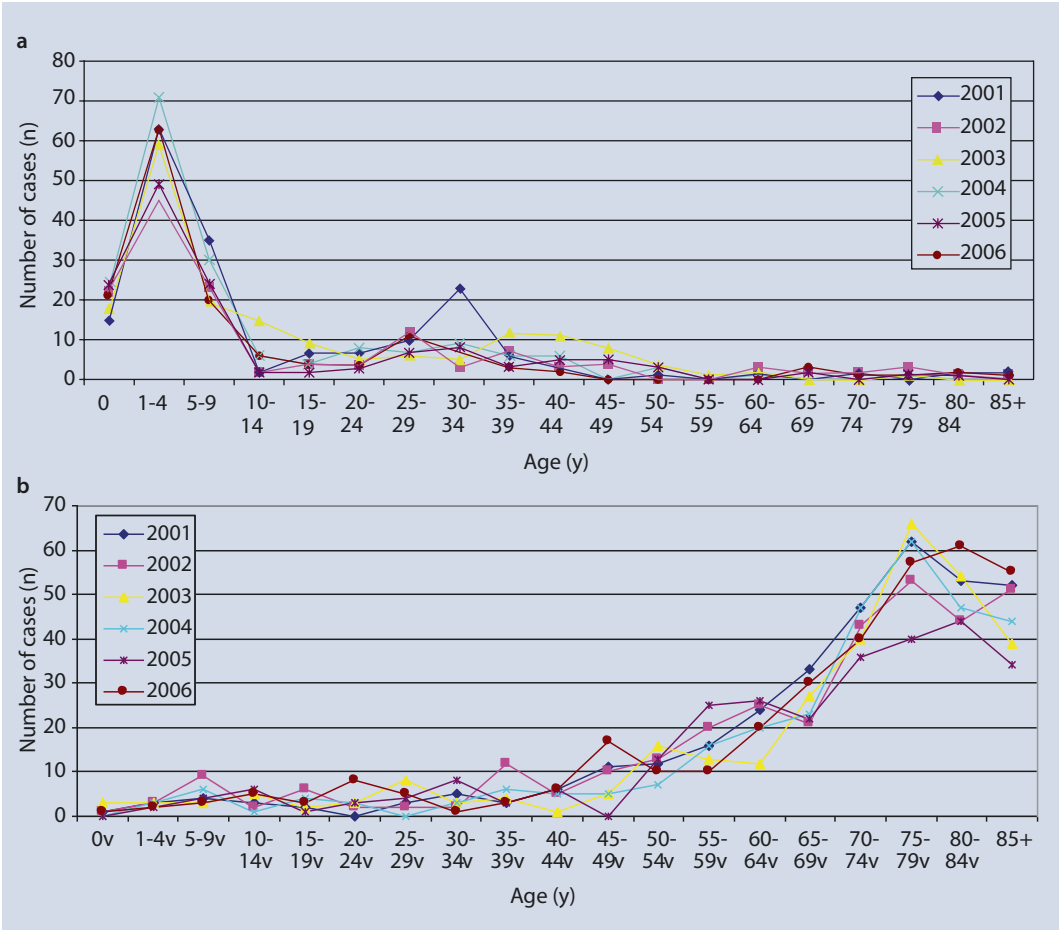


Fig. 10.1 **a** Outpatient clinic visits for varicella, Finland 2001–2006. **b** Hospital admissions for zoster, Finland 2001–2006. (From: ► https://www.julkari.fi/bitstream/handle/10024/103011/2008b40.pdf?sequence=1)

In Europe, the first varicella vaccine (Varilrix, GSK) was licensed for high-risk children in 1984 and, with a higher virus titer, for healthy children in 1995. For varicella vaccination of healthy children, Varilrix and Varivax (Merck) vaccines are available in Europe. Varivax is reported to have a virus concentration of 1350 Oka/Merck plaque forming units (pfu) and Varilrix $10^{3.3}$ Oka/RIT pfu (representing about 1995 pfu), i.e., the concentrations do not differ very much.

Live attenuated varicella vaccine induces a natural-like immunity, which is mediated through VZV-specific cellular and humoral immune responses. Evidence for the protective role of serum antibodies is indicated by a correlation between circulating VZV-specific antibody concentration and the probability of breakthrough varicella. Passive immunoprophylaxis by varicella zoster immunoglobulin after exposure to varicella also indicates the protective role of antibodies. VZV-specific cellular immunity is also associated with protection from VZV reactivation.

Pre-licensure studies of GSK's varicella vaccine showed that protection was dose-dependent, with a higher dose of varicella vaccine conferring higher protection and the protection being better against severe disease (Table 10.1). A more recent post-licensure efficacy trial found the efficacy of one dose of Varilrix to be 65%. In real-life outbreaks, the protection has been even lower. The post-introduction experience has resulted in the introduction of a second vaccine dose in most countries with a general varicella vaccination program.

Table 10.1 Efficacy of a single dose of high-titer and low-titer varicella vaccine (Varilrix®) with a follow-up of 2.5 years

Vaccine	Efficacy against varicella	
	Any severity	Moderately severe
High titer (7940 pfu)	88% (72–96)	100%
Low titer (2540 pfu)	55% (31–72)	

From: Varis and Vesikari (1996)

In 2006 and 2009, two doses of varicella vaccine to healthy children were recommended in the USA and in Germany, respectively. Two-dose vaccine recipients achieve up to 20-fold higher antibody levels and higher seroconversion rates than subjects receiving a single dose, and the booster effect is achieved irrespective of the time interval between administration of the first and second doses. The efficacy of two doses of either the Oka/Merck or the Oka/RIT strain is over 95% for any severity of varicella disease, at least for the first years after vaccination.

10.4 Vaccine Safety

The safety profile of the varicella vaccine in healthy subjects comes from preclinical studies and extensive post-marketing worldwide experience. The varicella vaccine may cause injection site reactions, including zoster-like localized rash in about 3–5% of immunized children. Additionally, a mild and transient generalized varicella-like rash may be seen. Rashes occur typically 5–26 days after immunization and usually consist of two to five lesions, mostly maculopapular rather than vesicular. However, most rashes that occur within the first 2 weeks after varicella immunization are due to wild-type VZV. Fever is common.

Description of Varilrix

► https://www.medicines.org.uk/emc/medicine/9787

Varilrix®[c] contains $10^{3.3}$ pfu (representing about 1995 pfu) of live attenuated varicella-zoster (Oka strain) virus propagated in MRC5 human diploid cells. The vaccine contains amino acids, human albumin, lactose, mannitol, and sorbitol. The solvent for reconstitution is Water for Injections. Two doses (each consisting of 0.5 ml of reconstituted vaccine) should be given, with an interval between doses of at least 6 weeks, but in no circumstances less than 4 weeks. One dose of Varilrix may be administered after a first dose of another varicella-containing vaccine.

Description of Varivax

► https://www.medicines.org.uk/emc/product/5582

The lyophilized vaccine contains sucrose, hydrolyzed gelatin, urea, sodium chloride, monosodium L-glutamate, anhydrous disodium phosphate, potassium dihydrogen phosphate, and potassium chloride.

When vaccination is initiated between 9 and 12 months of age, a second dose is needed and should be given after a minimum interval of 3 months.

In individuals aged between 12 months and 12 years, at least 1 month must elapse between the first and second doses.

Individuals 13 years of age and older should receive two doses with an interval of 4–8 weeks. If the interval between doses exceeds 8 weeks, the second dose should be given as soon as possible.

10.5 Post-Licensure Effectiveness of Varicella Vaccine (Live) (Oka/Merck Strain) in the USA

Five cross-sectional long-term surveys on varicella incidence, each from a random sample of approximately 8000 children and adolescents 5–19 years of age, were conducted over a period of 15 years in the USA, from 1995 (pre-vaccine) through 2009. Results showed a gradual decline in varicella incidence rates by 90–95% overall (approximately 10- to 20-fold) from 1995 to 2009 in all age groups, both in vaccinated and unvaccinated children and adolescents. In addition, a decrease by approximately 90% (approximately ten-fold) in varicella hospitalization rates was observed in all age groups. The estimated vaccine effectiveness (largely one dose only) over the study period was between 73% and 90%.

10.6 Post-Licensure Varicella Vaccine Effectiveness in Europe

In Europe, the greatest experience with post-licensure effectiveness data comes from Germany, which was the first European country to introduce universal varicella immunization (UVV) and at the same time have an active surveillance system to monitor the disease and its complications. Surveillance data indicate that in the first years after nationwide varicella vaccine implementation in 2004, the overall incidence of varicella decreased in two independent studies by 76–84% in children less than 19 years of age. Varicella hospitalization rates in the general population decreased between 2005 and 2012 by 60% in children and 40% in the adult population. Overall varicella vaccine effectiveness in preventing varicella disease (mild or severe) was 86% after dose 1 and 94% after dose 2. Moreover, sentinel data from April 2005 to May 2009 showed a reduction of 55% of varicella cases in all age groups, 63% in the age group 0–4 years, and 38% in 5- to 9-year-olds.

The very significant reductions in the incidence of varicella and varicella-associated complications observed in Germany have also been confirmed by regional data from other European countries that have implemented UVV programs, especially in those that have implemented a two-dose schedule coupled with a catch-up program and achieved a very high vaccination coverage. In all countries with a high vaccine coverage leading to a fast reduction of VZV circulation in the community, a significant reduction was observed in unvaccinated children younger than 1 year of age and older populations, indicating herd protection.

As of December 2020, Austria, Finland, Germany, Greece, and Luxembourg have UVV recommendations and programs at the national level and Italy at the regional level. Spain had implemented UVV in a few regions, but recently changed its policy and currently recommends the vaccine only for high-risk groups. Sixteen countries recommend targeted vaccination of susceptible adolescents and/or risk groups, 13 countries recommend vaccination for susceptible healthcare workers, and 4 for susceptible day-care personnel.

10.7 MMRV Vaccine

The combination of MMR plus varicella vaccine has been available since 2006. To make a proper combination, the titer of the varicella component in Merck's MMRV vaccine was increased from 1350 pfu to 9972 pfu for greater immunogenicity. Thus, the immunogenicity for VZV is higher after combined MMRV than after a single varicella vaccine (◘ Table 10.2). In GSK's MMRV vaccine, the varicella component has the same titer as in single varicella vaccine (1995 pfu). Two preparations of MMRV available are Priorix-Tetra® (GSK) and Pro-Quad® (Merck).

The reactogenicity of the MMRV combination is higher than after MMR vaccine given alone or separately, but concomitantly together with varicella vaccine (▶ Fig. 9.3). This is true for skin reactions, but particularly for high fever that occurs around days 5–12 after vaccination. In line with more frequent and higher fever, febrile convulsions also occur more frequently after MMRV than after MMR and varicella vaccine given sepa-

Table 10.2 Immune responses to two doses of a quadrivalent measles, mumps, rubella, and varicella vaccine in healthy children

	Pro-Quad $n = 381$		MMR and varicella separately $n = 390$	
	Seroconversion (%)	GMT	Seroconversion (%)	GMT
Measles	100	747	99.7	253
Mumps	100	286	99.7	97
Rubella	100	254	98.6	128
Varicella	99	469	93.1	16.5

From: Shinefield et al. (2005)
MMR measles–mumps–rubella, *GMT* geometric mean titer

rately. It is not clear if the two preparations of MMRV differ in this respect.

Universal varicella immunization programs may use monovalent varicella vaccine for the first dose to avoid the increase in febrile seizures associated with MMRV administration. MMRV is preferred for the second dose. The timing of the second dose of MMRV is more frequently determined by the MMR vaccination schedule. Germany and certain parts of Italy administer the second dose of MMRV at a 3-month interval. Such immunization schedules could enhance vaccine effectiveness, especially in the first years of UVV implementation because they can reduce more effectively the circulation of the VZV virus in the community and prevent breakthrough. It has been speculated that solid immunity against VZV might also be more likely to block subclinical infection by wild-type VZV, with ensuing latency.

10.8 Shift of Varicella Disease to Older Ages

Reduced circulation of wild-type VZV in the community owing to the use of varicella vaccine could be associated with an undesirable age shift of the incidence of varicella, associated with an increased severity of the disease, expected in older children, adolescents, pregnant women, and adults infected by VZV. So far, surveillance of varicella disease following the implementation of the two-dose schedules in European countries is reassuring; data show that the overall rates of varicella among adolescents and adults are declining and no age shift of varicella has been observed. However, data from seroprevalence studies indicate significant VZV immunity gaps among adolescents. Therefore, efforts at identifying susceptible adolescents for subsequent catch-up vaccination are critical to avoid the undesirable age shift of varicella to older ages, when varicella disease is more severe.

10.9 Impact of UVV on HZ

A significant concern with regard to the universal use of varicella vaccine is a possible effect of vaccination on the incidence of HZ, among both vaccinated and unvaccinated subjects.

In the vaccinated subjects, the vaccine virus may cause latent infection and remain in the dorsal root ganglia. The pathogenesis of HZ from the vaccine strain could be associated with a high concentration of the vaccine virus infecting the nerves at the vaccination site. It has been observed that the HZ rash in vaccinated children occurs more commonly in the dermatomes corresponding to the sites where the varicella vaccine was given.

However, real-life data from European countries have shown that the risk of developing zoster among the vaccinated population is significantly lower compared with that reported in children infected by wild-type varicella. This finding could be attributed to the lower viral loads in the vaccine and to the

reduced pathogenic capacity of the Oka strain compared with the wild-type virus. Nevertheless, long-term surveillance for HZ is required to confirm that the two-dose schedule establishes effective and long-lasting cellular immunity that will reduce the incidence of HZ among vaccinated subjects.

More significant concerns have been associated with a possible increase in HZ among subjects that have already been infected with the wild-type virus. Re-exposure to VZV through contact with an infected person may boost VZV cellular immunity and increase protection against HZ, and in areas with UVV, the incidence of HZ could increase owing to reduced exposure to varicella.

Nevertheless, real-life experience has indicated only a slight increase or no increase in HZ incidence in areas where universal varicella vaccination has been implemented, comparable with countries where no UVV has been implemented. Such a discrepancy between the predicted increase in HZ and the real-life situation suggests that silent reactivation of the wild-type virus might be associated with endogenous boosting of cellular immunity and might be more important in maintaining latency rather than immunity from exogenous boosting.

10.10 Varicella Vaccine Recommendations for Special Groups

After licensure, the varicella vaccine was primarily intended for the vaccination of high-risk groups, such as children with leukemia or cancer. However, live varicella vaccine today is contraindicated in individuals with immunosuppression because of the high rate of adverse effects and because it is necessary to temporarily stop chemotherapy for varicella vaccination. Instead, varicella vaccine is now recommended for:

- Childhood candidates for solid organ transplant with no history of chickenpox (or unclear) 6 months before surgery, with undetectable antibodies.
- Seronegative subjects in remission from malignancies.
- Adolescents 12–18 years or older and women of childbearing age with no history of varicella.
- People in contact with immunosuppressed patients.
- Healthcare workers.
- Child care workers.
- Laboratory staff.
- As post-exposure prophylaxis (given within 72 h of exposure).

10.11 Contraindications to Varicella Vaccine

Varicella vaccine is contraindicated in:

- Subjects with primary or acquired immunodeficiency states with a total lymphocyte count less than 1200 per mm^3.
- Severe humoral or cellular primary immunodeficiencies, e.g., severe combined immunodeficiency.
- Subjects with a lack of cellular immune competence, such as leukemia, lymphoma, blood dyscrasia.
- Individuals receiving immunosuppressive therapy including high-dose corticosteroids.
- Patients who clinically manifest AIDS or symptomatic HIV infection or have low age-specific CD4+ T-lymphocyte counts.
- Active untreated tuberculosis.
- Pregnancy and breast-feeding (pregnancy should be avoided for 1 month following vaccination).

Transmission of the vaccine virus from vaccinees to susceptible contacts has rarely been shown to occur and has been associated with vaccine-associated cutaneous lesions. Therefore, contact with high-risk individuals must be avoided if the vaccinee develops a cutaneous rash likely to be vaccine-related within 4–6 weeks of the first or second dose and until this rash has completely disappeared. In the absence of a rash in the vaccinee, the risk of transmission of the vaccine viral strain is deemed nonexistent.

10.12 Herpes Zoster Vaccine

The first vaccine against HZ (Zostavax®, Merck) was licensed in 2006. The vaccine is essentially a concentrated form of Varivax® containing 14 times more live VZV. In addition, it contains an unknown quantity of non-live varicella antigenic material. However, because of the live virus, Zostavax® cannot be given to immunocompromised persons.

The efficacy of Zostavax against HZ in the age group 50–59 years is about 70% and decreases with increasing age. Several European countries, including the UK, France, and two federal states of Germany, recommend the use of Zostavax® in various older age groups.

A new non-live vaccine against HZ (Shingrix®), constituting of VZV glycoprotein E combined with an adjuvant, was recently developed by GSK. This vaccine, given in two doses, has shown efficacy of 90–97%. As a non-live vaccine, Shingrix® could be given to immunocompromised subjects and may also become available for pediatric use in selected patients who experience HZ at an early age. The licensure of Shingrix® is expected in 2017.

Further Reading

Bonanni P, Gershon A, Gershon M, Kulcsar A, Papaevangelou V, Rentier B, et al. Primary versus secondary failure after varicella vaccination: implications for interval between 2 doses. Pediatr Infect Dis J. 2013;32(7):e305–13.

Bozzola E, Tozzi AE, Bozzola M, Krzysztofiak A, Valentini D, Grandin A, et al. Neurological complications of varicella in childhood: case series and a systematic review of the literature. Vaccine. 2012;30(39):5785–90.

Cunningham AL, Heineman T. Vaccine profile of herpes zoster (HZ/su) subunit vaccine. Expert Rev Vaccines 2017;16:1−10.

European Medicines Agency. Monovalent and multivalent measles, mumps, rubella and/or varicella vaccines 2012 [cited 2013]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/MMRV/human_referral_000334.jsp&mid=WC0b01ac05805c516f#documents.

Hagemann C, Krämer A, Grote V, Liese JG, Streng A. Specific Varicella-Related Complications and Their Decrease in Hospitalized Children after the Introduction of General Varicella Vaccination: Results from a Multicenter Pediatric Hospital Surveillance Study in Bavaria.

Harder T, Siedler A. Systematic Review and Meta-analysis of Chickenpox Vaccination and Risk of Herpes Zoster: A Quantitative View on the "Exogenous Boosting Hypothesis". Clin Infect Dis. 2019 Sep 27;69(8):1329−1338.

Klein NP, Fireman B, Yih WK, Lewis E, Kulldorff M, Ray P, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics. 2010;126(1):e1–8.

Knuf M, Zepp F, Meyer CU, Habermehl P, Maurer L, Burow HM, et al. Safety, immunogenicity and immediate pain of intramuscular versus subcutaneous administration of a measles-mumps-rubella-varicella vaccine to children aged 11–21 months. Eur J Pediatr. 2010;169(8):925–33.

Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med. 2015;372:2087–96.

Marin M, Marti M, Kambhampati A, Jeram SM, Seward JF. Global Varicella Vaccine Effectiveness: A Meta-analysis. Pediatrics. 2016 Mar;137(3):e20153741.

Marin M, Leung J, Gershon AA. Transmission of Vaccine-Strain Varicella-Zoster Virus: A Systematic Review. Pediatrics. 2019 Sep;144(3):e20191305.

Mészner Z, Wysocki J, Richter D, Zavadska D, Ivaskeviciene I, Usonis V, et al. Burden of varicella in Central and Eastern Europe: findings from a systematic literature review. Expert Rev Vaccines : 2019 Mar;18(3):281−293.

Michael Povey , Ouzama Henry, Marianne A Riise Bergsaker, Roman Chlibek, Susanna Esposito, et al Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine or one dose of monovalent varicella vaccine: 10-year follow-up of a phase 3 multicentre, observer-blind, randomised, controlled trial: Lancet Infect Dis 2019 Mar;19(3):287−297.

Ogunjimi B, Van Damme P, Beutels P. Herpes zoster risk reduction through exposure to chickenpox patients: a systematic multidisciplinary review. PLoS One. 2013;8(6):e66485.

Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med. 2005;352:2271–84.

Riera-Montes M, Bollaerts K, Heininger U, Hens N, Gabutti G, Gil A, Nozad B, Mirinaviciute G, Flem E, Souverain A, Verstraeten T, Hartwig S. Estimation of the burden of varicella in Europe before the introduction of universal childhood immunization. BMC Infect Dis. 2017 May 18;17(1):353.

Shinefield H, Black S, Williams WR, et al. Dose-response study of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children. Pediatr Infect Dis J. 2005;24(8):670–5.

Siedler A, Arndt U. Impact of the routine varicella vaccination programme on varicella epidemiology in Germany. Euro Surveill. 2010;15(13).

Siedler A, Dettmann M. Hospitalization with varicella and shingles before and after introduction of childhood varicella vaccination in Germany. Hum Vaccin Immunother. 2014;10(12):3594−600.

Spackova M, Muehlen M, Siedler A. Complications of varicella after implementation of routine childhood varicella vaccination in Germany. Pediatr Infect Dis J. 2010;29(9):884–6.

Spoulou V, Alain S, Gabutti G, Giaquinto C, Liese J, Martinon-Torres F, Vesikari T. Implementing Universal Varicella Vaccination in Europe: The Path Forward .Pediatr Infect Dis J. 2019 Feb;38(2):181−188.

Takahashi M, Otsuka T, Okuno Y, Asano Y, Yazaki T. Live vaccine used to prevent the spread of varicella in children in hospital. Lancet. 1974;2(7892):1288–90.

Varis T, Vesikari T. Efficacy of high-titer live attenuated varicella vaccine in healthy young children. J Infect Dis. 1996;174(Suppl 3):S330–4.

Weinmann S., Irving SA, Koppolu P, Naleway AL et al. Incidence of herpes zoster among varicella-vaccinated children, by number of vaccine doses and simultaneous administration of measles, mumps, and rubella vaccine. Vaccine . 2020 Aug 18;38(37):5880−5884.

Woodward M, Marko A, Galea S, Eagel B, Straus W. Varicella Virus Vaccine Live: A 22-Year Review of Postmarketing Safety Data. Open Forum Infect Dis. 2019 Aug 1;6(8):ofz295.

Wutzler P, Casabona G, Cnops J, Akpo E, Safadi M. Herpes zoster in the context of varicella vaccination – an equation with several variables. Vaccine 2018;36:7072−82.

Wutzler P, Bonanni P, Burgess M, Gershon A, Safadi M, Gasabona G. Varicella vaccination – The global experience. Expert Rev Vaccines 2017;16:833−43.

Zoch-Lesniak B, Tolksdorf K, Siedler A. Trends in herpes zoster epidemiology in Germany based on primary care sentinel surveillance data, 2005-2016. Hum Vaccin Immunother. 2018 Jul 3;14(7):1807–1814.

Rotavirus Vaccine

Timo Vesikari

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_11

11.1 Burden of Rotavirus Disease

The clinical characteristics of severe rotavirus (RV) gastroenteritis (RVGE) include watery diarrhea, frequent vomiting, and high fever. About 20–30% of all children experience a clinically manifest episode of RVGE, and 10–20% of these (2–3% of all) are severe. Prevention of severe RVGE is the primary target of RV vaccination. In Europe, RV causes about one half of severe acute gastroenteritis (GE) in childhood requiring hospitalization. On average, RVGE is more severe than gastroenteritis caused by other viruses.

Moreover, it is now recognized that RV often causes a systemic infection and RV antigen and RNA can be detected in the circulation. RV vaccination also prevents some 20% of all febrile seizures. Rather than gastroenteritis, it is more appropriate to talk about RV disease. Prevention of RV disease by vaccination is a neutral term that puts RV vaccine in the same category as other viral vaccines, in contrast to being a "diarrheal disease vaccine."

Still, the first target of RV vaccination in Europe is the prevention of severe RVGE and, specifically, hospitalizations for RVGE. Hospital admission is also the major factor (about 90%) in calculations of financial burden associated with RVGE. The number of annual hospitalizations in Europe was at least 87,000 before RV vaccination was introduced. The rate of hospitalizations may vary according to local clinical practices, but there are probably also true differences between countries. For Europe, it has been estimated that the risk of hospitalization for RVGE before the age of 5 is 1 in 54, with a high of 1 in 33 in Finland and low of 1 in 67 in Denmark. It is plausible that in countries with long, cold winters, the RV season is longer and severe RVGE more common.

Some countries with a relatively low incidence of RVGE, such as Denmark and the Netherlands, have considered that there is no need to introduce RV vaccination into the immunization program. However, even if a country has decided not to introduce universal RV vaccination, at an individual level, the risk of severe RVGE in any European country is high enough to warrant prevention by vaccination.

Deaths from RVGE are rare in Europe (a 2006 estimate was 231 for European Union countries), but deaths may occur in cases of delayed admission to care. RVGE is still a potentially fatal disease in Europe, and the low mortality is only attributable to the availability of good case management at outpatient and hospital facilities.

Globally, RV is a major cause of childhood mortality. A recent estimate before large-scale RV vaccinations put the number of RV-associated deaths at 197,000 a year. Of individual countries, India had the highest number of deaths, followed by Nigeria, Pakistan, Bangladesh, and Indonesia. Introduction of RV vaccination in the high-mortality countries is a global public health priority, but has been slow in the named countries.

11.2 RV Epidemiology

Almost all RVs causing disease in humans belong to group A, determined by the common inner core group antigen VP6. VP6 is the most abundant protein in the RV particle and a powerful immunogen, and immune reaction against this antigen is likely the major mechanism of protection against severe RV disease. Protection may be induced by natural RV infection or vaccination alike. It takes two or three infections, or "hits," to induce solid protection against severe disease; the "hits" may also be administered in two or three doses of oral vaccine, and the protection is limited to RV disease and not infection. Protection against RV infection depends on immunity against the VP7 and VP4 surface antigens, and such protection is more variable and not durable.

The two surface antigens VP7 and VP4 determine the G- and P-types of RVs, respectively, and induce neutralizing antibodies. Although a large number of G- and P-combinations are possible, in reality a few fixed combinations prevail. The most common RV types are G1P[8], followed by G2P[4],

G3P[8], G4P[8], G9P[8], and, more recently, G12P[8]. Altogether, RV diversity has increased after RV vaccinations, but this has not reduced the effectiveness of the vaccine against severe RVGE, which is largely not dependent on immunity to G- or P-types. The surface antigen-induced antibodies protect against RV infection and have an effect on the RV strains that are prevalent in circulation, but the serotype-specific antibodies are not critical for the protection against severe RV disease.

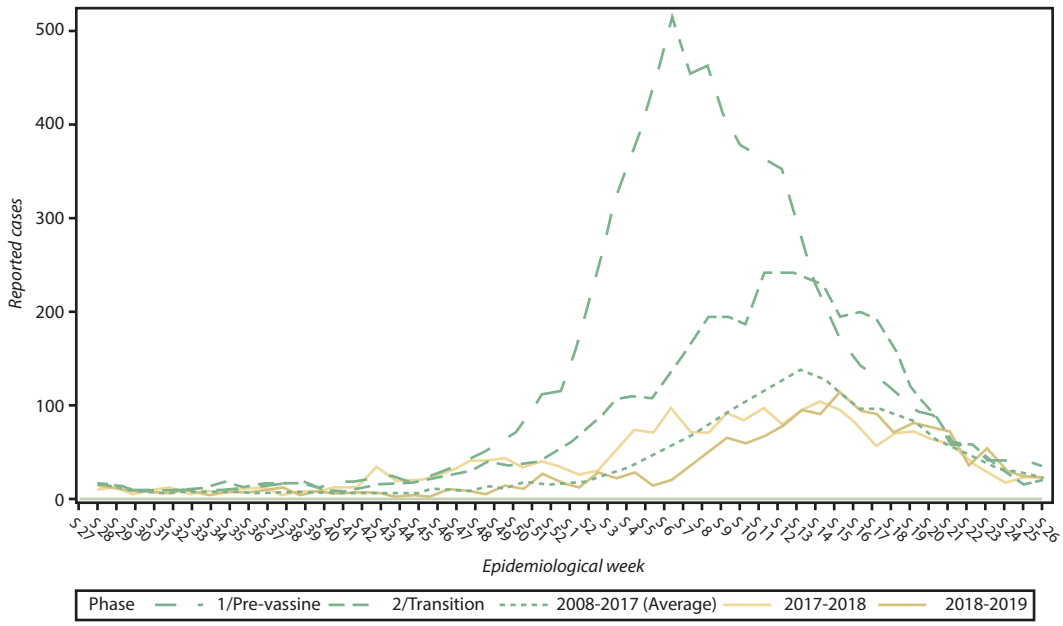
Although the predominant RV types vary by the year, no single type is predominant in the whole of Europe at the same time. Rather, there are multiple types of RV circulating at the same time in different regions. Thus, the rotavirus epidemic (season) does not have a single origin either, but RVs become prevalent in the winter season at various locations independently. Still, the seasonal pattern was very predictable until the introduction of universal RV vaccinations. In the countries with a high coverage of vaccinations, the RV season has shifted from peak winter toward spring and summer as first observed in Europe in Belgium (◘ Fig. 11.1).

Most cases of severe RV disease in Europe occur in the age group 6–18 months, i.e., in the first winter epidemic season of life. Therefore, vaccination schedules need to be completed by the age of 6 months. With introduction of vaccinations, there has been a shift in age distribution as discussed in ▶ Sect. 11.7 (◘ Fig. 11.2).

11.3 RV Vaccines

All RV vaccines are live attenuated tissue culture-grown RVs of human or animal origin or reassortants of human and animal

◘ **Fig. 11.1** Oral administration of rotavirus (RV) vaccine



◘ **Fig. 11.2** Rotavirus epidemic season with a winter peak before vaccination and the blunted peak after vaccinations in Belgium. (*Source*: sentinel lab Sciensano (Belgium))

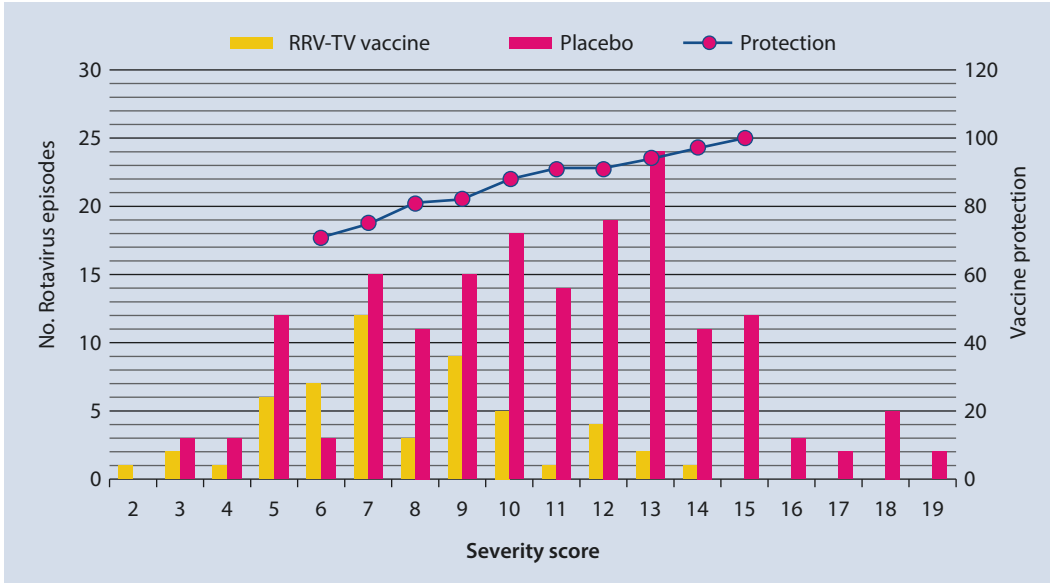


Fig. 11.3 Rotavirus disease severity and rhesus rotavirus tetravalent vaccine protection (Joensuu et al. 1997; Ruuska and Vesikari 1990)

RVs. RV vaccines are given orally (Fig. 11.1) to multiply in the intestine and to mimic asymptomatic wild-type RV infection. Vaccine virus infection is likely to induce natural-like immunity against RV disease, even if the mechanism of protection is not fully known.

The first experimental RV vaccine was a bovine rotavirus that was found to infect humans and to induce a high level of cross-protection against severe human RVGE in spite of having "non-human" G- and P-types. The early studies of bovine RV vaccine in the 1980s established some general principles of RV vaccination, which have been confirmed subsequently in numerous studies with other live RV vaccines: (1) vaccine-induced protection is higher against severe RVGE than any (including mild) RV disease; (2) oral RV vaccine needs to be given with a buffer because gastric acid may inactivate RV and reduce the uptake of RV vaccine; (3) breast milk or breast-feeding (despite RV IgA in the breast milk) does not negatively affect the uptake of RV vaccine; and (4) simultaneous administration of oral poliovirus vaccine (OPV) may interfere with live RV vaccine.

The first licensed RV vaccine (RotaShield®, Wyeth) in 1998 in the USA was a rhesus-human reassortant "tetravalent" vaccine, which contained three reassortants of rhesus rotavirus with human G-types G1, G2, and G4 plus the rhesus RV (G3) itself. This vaccine was given in three doses and after a full series induced a high level of protection, as shown in Fig. 11.3. With the use of a 20-point severity scale ("Vesikari scale"), the protection level against different severities of RVGE was determined with a greater accuracy. The protection reached 100% against disease with a severity score of 15/20; using the most commonly applied cutoff score of 11/20 for severe RVGE, the protection was about 90%. The same scale has been used to measure protection of other RV vaccines as well.

RotaShield® induced febrile reactions in about one third of the recipients and about 3% had high fever. After a million doses given in the USA by 1999, the vaccine was found to be associated with intussusception (IS) and was withdrawn. Other rotavirus vaccines are not reactogenic like RotaShield®. Still, the current RV vaccines may also cause IS, even though the risk is lower than that associated with RotaShield®.

The current major licensed RV vaccines are human RV vaccine (Rotarix™, GSK) and bovine–human reassortant RV vaccine (RotaTeq®, Merck), both of which are available and widely used in Europe and globally. The recommendations of the European Society for Pediatric Infectious Diseases (ESPID) take the position that both vaccines can be recommended to protect European children from RVGE and that the performance of the vaccines in Europe is equal. No formal head-to-head comparison of the vaccines has been done.

11.4 Human RV Vaccine Rotarix™

Human RV vaccine (Rotarix™, GSK), also termed RV1, is the most extensively used RV vaccine today. It was derived from a G1P[8] RV isolate in Cincinnati, passaged 33 times in cell culture and designated 89–12. The strain was acquired by GSK, cloned (by plaque purification) and passaged another 12 times in MRC-5 cells. In this process, the virus lost its residual reactogenicity and is generally regarded as nonreactogenic for humans. Rotarix™ multiplies effectively in humans, as characterized by a high rate of shedding (60% or even more) after the first dose, but does not cause diarrhea or systemic reactions; in other words, it is highly attenuated for its original host.Rotarix™ is given in two doses. The uptake and immunogenicity are excellent (90%) even after the first dose when given in the presence of a low level of maternal antibody, such as in European populations. The uptake of the second dose may be prevented by the antibodies induced after the first dose, as indicated by the lack of shedding and lack of a booster response after the second dose. Therefore, the second dose mainly fills the immunity gap remaining after the first dose, but does not induce an increase in the level of antibodies if the first dose has been successful. The pivotal safety and efficacy trial for licensure was carried out in 60,000 children in Latin America. Before licensure in Europe, the vaccine was tested in five European countries. Rotarix™ was the first new RV vaccine to be licensed after the withdrawal of RotaShield®, with European licensure in 2006.

The results of the major European efficacy trial of Rotarix™ are illustrative for the performance of this vaccine. The primary endpoint was severe RVGE, as defined by score 11/20. Against such severe RVGE, the efficacy for 2 years was 91%, with 96% efficacy in the first season and 86% in the second season, showing a decline over time. Against any RVGE the efficacy was 78% and 68% in the first and second year, respectively, for a total efficacy of 72% over 2 years. The efficacy against severe RVGE by G-type ranged from 96% for G1P[8] to 86% for G2P[4]; these differences were not statistically significant (Fig. 11.4a). For any RVGE, the efficacy point estimates were higher for G1, G3, G4, and G9 with P[8] than G2P[4] with 58%. The interpretation would be that a G1P[8] vaccine cannot well control the circulation of G2P[4] RV, but remains efficacious against severe RVGE caused by this "fully heterotypic" RV. G2P[4] has often become more prevalent after universal RV vaccination with Rotarix.

Description of Rotarix™ According to the Summary of Product Characteristic (SPC)

► https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Rotarix/pdf/ROTARIX-PI-PIL.PDF

ROTARIX, for oral administration, is a live, attenuated rotavirus vaccine derived from the human 89–12 strain, which belongs to the G1P[8] type. The rotavirus strain is propagated on Vero cells. After reconstitution, the final formulation (1 mL) contains at least 10^6 median Cell Culture Infective Dose (CCID50) of live, attenuated rotavirus.

The lyophilized vaccine contains amino acids, dextran, Dulbecco's Modified Eagle Medium (DMEM), sorbitol, and sucrose. DMEM contains the following ingredients: sodium chloride, potassium chloride, magnesium sulfate, ferric (III) nitrate, sodium phosphate, sodium pyruvate, D-glucose, concentrated vitamin solution, L-cystine, L-tyrosine, amino acids solution, L-glutamine, calcium chloride, sodium hydrogencarbonate, and phenol red.

In the manufacturing process, porcine-derived materials are used. Porcine circovirus type 1 (PCV-1) is present in ROTARIX. PCV-1 is not known to cause disease in humans.

The liquid diluent contains calcium carbonate, sterile water, and xanthan. The diluent includes an antacid component (calcium carbonate) to protect the vaccine during passage through the stomach and prevent its inactivation owing to the acidic environment of the stomach.

ROTARIX is available in single-dose vials of lyophilized vaccine, accompanied by a prefilled oral applicator of liquid diluent. The tip caps of the prefilled oral applicators may contain natural rubber latex; the vial stoppers are not made with natural rubber latex.

ROTARIX contains no preservatives.

11.5 Bovine–Human Reassortant RV Vaccine, RotaTeq®

The "pentavalent" bovine–human reassortant RV vaccine (RotaTeq®, Merck, also termed RV5) is a combination of four G-type reassortants (for G1–G4) and one P-type (P[8]) reassortant on the WC-3 bovine RV genetic backbone. As WC-3 is a G6P[5] virus, these bovine G- and P-types are also present in the vaccine. The terms "pentavalent" and RV5 refer to the five mono-reassortant strains in the vaccine. However, it is now well established that the protection against severe RVGE induced by the vaccine is not limited to the G or P types contained in the product (see below).The RotaTeq® vaccine is given in three doses. This was determined early on to accommodate the US childhood immunization program (2, 4, and 6 months of age), but has an additional basis in the demonstration of incremental immunogenicity and protection by each dose. RotaTeq® vaccine virus is also shed after vaccination, and the shedding may rarely be associated with diarrhea. The G1 and P[8] reassortants included in the RotaTeq® vaccine may re-reassort with each other and form vaccine-derived (vd) double reassortants on the bovine RV VP6 core, which may be more virulent than the original single reassortant vaccine viruses, and vdG1P[8] may be responsible for most of the diarrhea seen after vaccination in about 1% of the vaccine recipients.

The efficacy and safety of the RotaTeq® vaccine were established in the large (70,000 infants) Rotavirus Efficacy and Safety Trial (REST). The overall efficacy against severe RVGE as determined by healthcare utilization (combined endpoint of hospital admission and outpatient clinic treatment) was 95%

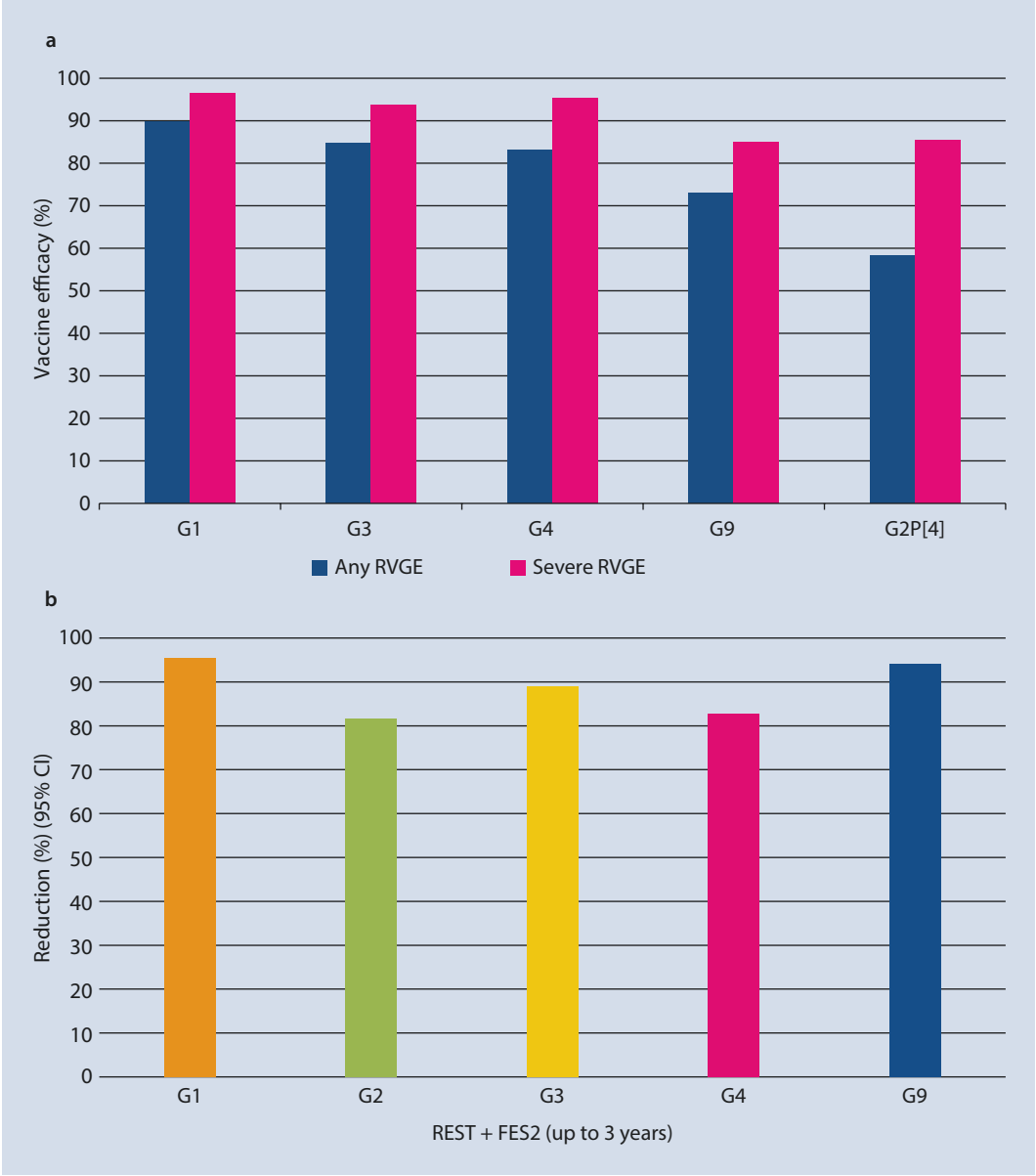


Fig. 11.4 **a** European efficacy trial of Rotarix. Vaccine efficacy against rotavirus gastroenteritis (RVGE) caused by specific RV types. **b** Finnish Extension Study of Rotateq vaccine: serotype-specific efficacy of RV5 against hospitalizations and emergency department visits

(Fig. 11.4b). An extension study of the REST in Finland involving 21,000 children confirmed that RotaTeq was efficacious against severe RVGE associated not only with G1, G3, and G4, all P[8], but also against G9P[8], which is not among the G-types in the vaccine, and G2 P[4], with a different P-type. RotaTeq® was licensed in 2006 and is now one of the two major RV vaccines used globally.

Description of RotaTeq® According to the SPC

► http://www.merck.com/product/usa/pi_circulars/r/rotateq/rotateq_pi.pdf

RotaTeq is a live, oral pentavalent vaccine that contains five live reassortant rotaviruses. The rotavirus parent strains of the reassortants were isolated from human and bovine hosts. Four reassortant rotaviruses express one of the outer capsid proteins (G1, G2, G3, or G4) from the human rotavirus parent strain and the attachment protein (serotype P7) from the bovine rotavirus parent strain. The fifth reassortant virus expresses the attachment protein, P1A (genotype P[8]), herein referred to as serotype P1A[8], from the human rotavirus parent strain and the outer capsid protein of serotype G6 from the bovine rotavirus parent strain.

The reassortants are propagated in Vero cells using standard cell culture techniques in the absence of antifungal agents.

The reassortants are suspended in a buffered stabilizer solution. Each vaccine dose contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, and trace amounts of fetal bovine serum. RotaTeq contains no preservatives.

In the manufacturing process for RotaTeq, a porcine-derived material is used. DNA from porcine circoviruses (PCV) 1 and 2 has been detected in RotaTeq. PCV-1 and PCV-2 are not known to cause disease in humans.

RotaTeq is a pale yellow clear liquid that may have a pink tint.

The plastic dosing tube and cap do not contain latex.

11.6 Comparative Efficacy

Both the Rotarix™ and the RotaTeq® vaccines have been tested for efficacy in different environments, from developed to "intermediate" to developing countries. In general, the overall and serotype-specific efficacy against severe RVGE of the two vaccines are remarkably similar in all settings, being highest in Europe (around 95%) followed by Latin America (80–85%) and Africa (50–70%). No formal head-to-head comparative efficacy trial has been conducted. In a recent comparative immunogenicity study in the USA, three doses of RotaTeq® was more immunogenic by RV IgA response than two doses of Rotarix™. The same study showed that a mixed schedule of two doses of RotaTeq® and one dose of Rotarix™ was even more immunogenic.

11.7 Real-Life Effectiveness

Studies on the real-life effectiveness of RV vaccines after the introduction of immunization programs have been conducted in several countries and areas. On the whole, there seems to be a similar gradient in vaccine effectiveness to that in prelicensure efficacy trials among developed, "intermediate," and developing countries.

In Europe, the examples of Finland and Belgium are representative. In these countries, which have reached a high coverage with RV5 (Finland) and RV1 (Belgium), respectively, the real-life vaccine effectiveness in the target population has been well above 90% against hospitalization for RVGE. In Austria, with coverage of 72–74%, the reduction of RVGE hospitalizations in the target age group was 81–84%, and this was sustained for up to 3 years. The direct impact of RV vaccination in the target age group has shifted the occurrence of RVGE to older unvaccinated children (◘ Fig. 11.5).

The indirect effect of RV vaccinations on unvaccinated children remains unsettled. In Austria, there was initially an indirect effect on unvaccinated children, but after 3 years, this was followed by an increase in RVGE hospitalizations in 5- to 14-year-old children. In Finland, with an RV vaccination coverage of 95%, the reduction in cases of RVGE seen in hospitals was 94% in a period of 4 years after vaccination, but specifically in the age group 5–14 years, no significant reduction was seen over this period. It seems that large-scale RV

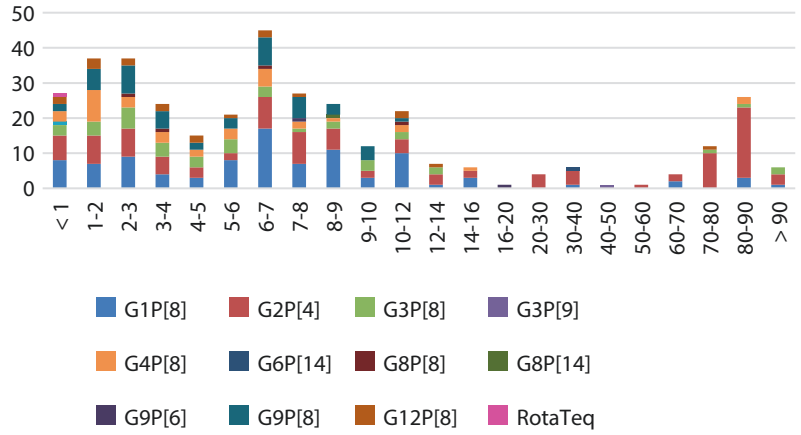


Fig. 11.5 Age distribution and associated genotypes in all RVGE cases in Finland after universal RV vaccinations. (Adapted from Markkula et al. (2020))

vaccinations interrupt the circulation of wild-type RVs after initial introduction, but do not eliminate RV circulation. Over time, the circulating wild-type RVs find susceptible individuals, and some of these will come down with severe RVGE. In addition, RV circulates and causes small outbreaks of disease in the elderly, seemingly unaffected by vaccination of children (Fig. 11.5).

The impact of vaccines on all hospitalizations due to acute gastroenteritis depends on the share of RV in all severe gastroenteritis and the vaccine coverage. At best, the total reduction of hospitalizations from any gastroenteritis may be as high as 70%, as observed in Finland over a period of 4 years.

11.8 Effects beyond Gastroenteritis

Over the years since introduction, it has become clear that RV vaccination has positive effects beyond prevention of acute gastroenteritis. RV causes a systemic infection with high degree of antigenemia and low degree of viremia. Severe RVGE may be associated with seizures. RV vaccination has been found to decrease all seizures in children by 20% or more.

RV vaccination has also been shown to prevent chronic disease. An extension study of REST in Finland found that RV vaccination reduced celiac disease by one third and possibly stopped the increase of type 1 diabetes (DM1) (Fig. 11.8). A US study found a reduction of 3–4% in the incidence of DM1 in young children in the time since the introduction of RV vaccination.

The impact on DM1 and celiac disease beyond RVGE is of such magnitude that they provide an additional argument for introduction of universal RV vaccination (Fig. 11.6).

11.9 Introduction of RV Vaccination

After Austria (both vaccines), Belgium (Rotarix™), and Finland (RotaTeq® exclusively), there was a gap of a couple of years until Germany started universal vaccinations state by state. The most significant recent step forward is perhaps the introduction into the UK in 2014. The map in Fig. 11.7 shows the status of universal RV vaccinations in Europe in 2020.

No country that has initiated a universal program has stopped it. However, in 2015, France recalled the recommendation for RV vaccination over concerns of safety (IS) and is unlikely to relaunch a universal RV vaccination program. Spain has withdrawn the Rotarix vaccine for concerns over porcine circovirus (PCV-1) contamination (see below).

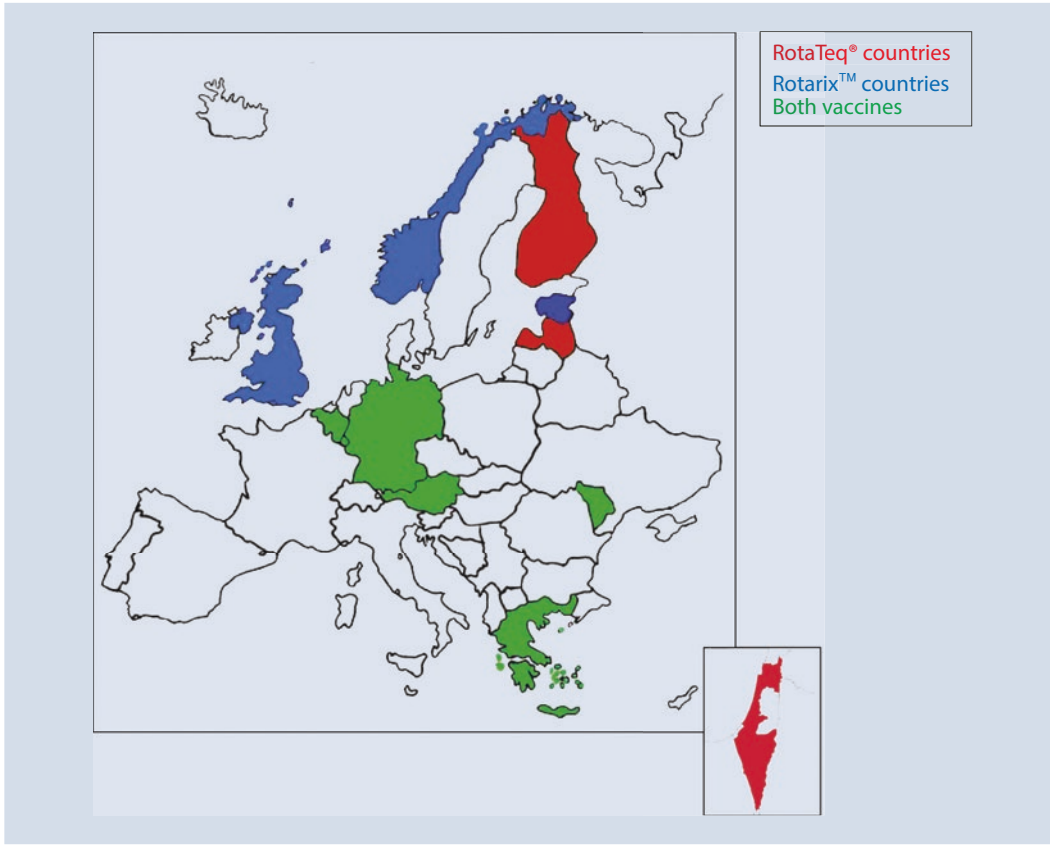


Fig. 11.7 Universal RV vaccination programs in Europe

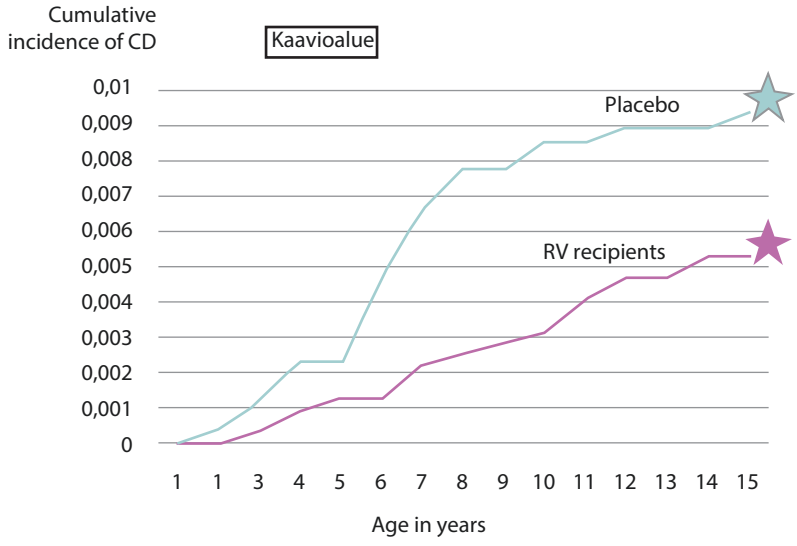


Fig. 11.6 Reduction in celiac disease between ages 11 and 14 years in children participating in REST study and receiving RotaTeq vaccine or placebo. (Adapted from Hemming-Harlo et al. (2019))

11.10 Intussusception

Intussusception is the most important adverse effect of RV vaccination. Association with IS led to the withdrawal of the first licensed RV vaccine, RotaShield®, in 1999. IS occurred mostly 3–7 days after the first dose of RotaShield®, and the attributable risk was estimated at 1:10,000. However, the risk of IS was shown to be age-dependent, and most of the cases occurred in the catch-up vaccination program in infants who were over 90 days of age at the time of the first dose.

Both of the leading licensed RV vaccines, Rotarix™ and RotaTeq®, are also associated with IS, albeit with a lower risk than RotaShield®. The prelicensure trials did not detect the risk, as they were designed to rule out a risk of IS of similar magnitude to that with RotaShield®. Later, in a post-marketing surveillance study, the risk estimates of IS for both vaccines are between 1:50,000 and 1:80,000 after the first dose.

The age pattern of RV vaccine-associated IS, whether by RotaShield® or the current vaccines, may follow that of naturally occurring IS (Fig. 11.6). Therefore, it is important not to administer the first dose of any RV vaccine after 90 days of age, but it is prudent to follow the current ESPID recommendation and give the first dose of RV vaccine as early as possible, i.e., at 6–8 weeks of age (Fig. 11.8).

The small risk of IS is often weighed against the benefits of RV vaccination, and this comparison comes out in favor of vaccination in developed countries as well. However, everything should be done to minimize the risk, and early administration of the first dose is of key importance.

11.11 Porcine *Circovirus*

In 2010, both licensed RV vaccines were found to have porcine *circovirus* (PCV) as a contaminant. PCV is not known to infect humans, and the WHO and European Medicines Agency have held that RV vaccines may continue to be used. Some European countries withdrew Rotarix™ temporarily, but this position is maintained only in Spain. In Rotarix™, PCV contamination was traced to virus seed, but the manufacturer is committed to providing a PCV-free vaccine in the future.

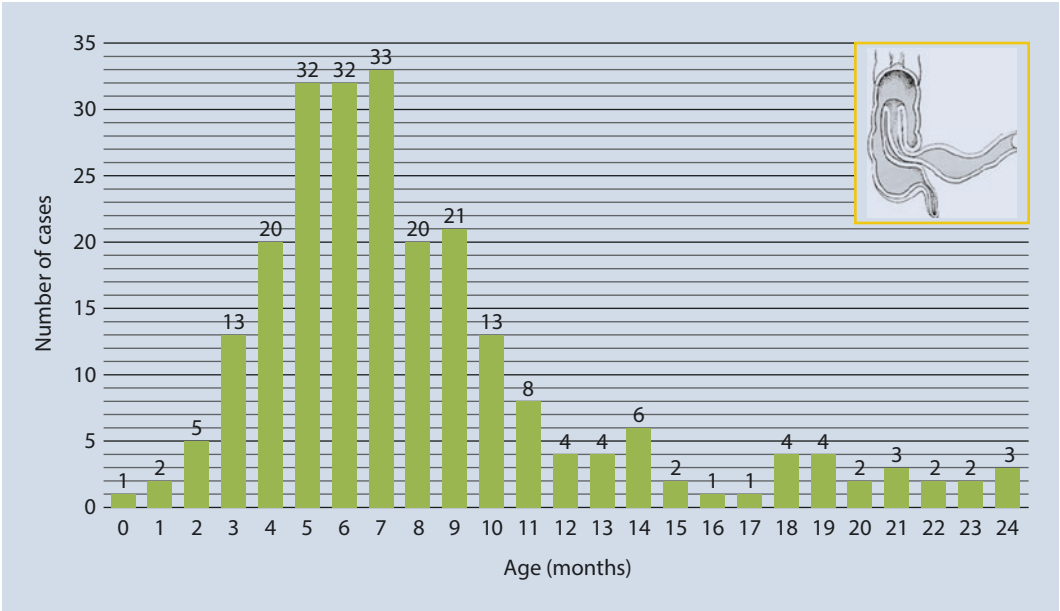


Fig. 11.8 Age distribution of naturally occurring intussusception in Finnish children. Timo Vesikari, unpublished

In RotaTeq®, the source of contamination was traced to batches of trypsin used in the manufacturing process, and with changes in the process, PCV-free vaccine should be available. However, at the present time neither RV vaccine is explicitly PCV-free.

11.12 RV Vaccine Recommendations

In Europe, there is no formal recommendation-issuing body, but the pediatric societies, the ESPID and the European Society for Paediatric Gastroenterology Hepatology and Nutrition, issued recommendations in 2008 that were updated as ESPID recommendations in 2015. The US Advisory Committee on Immunization Practices recommendations are also widely followed. Globally, the most important one is the WHO position for universal recommendation.

All major recommendations hold that RV vaccination should be given to all children, because no special "risk groups" for RVGE can be identified. However, two European countries, Croatia and the Netherlands, make an exception of the rule and recommend RV vaccination for only "high risk groups," including prematurely born infants.

11.12.1 Premature Infants

Both RotaTeq® and Rotarix™ vaccines can be given to prematurely born infants regardless of gestational age, following the recommendations according to calendar age. If the infant is still in hospital, a possible risk of transmission of the vaccine virus must be considered.

11.12.2 HIV-Infected Children

Asymptomatic HIV-infected infants can be vaccinated normally according to calendar age without any safety issues using either Rotarix™ or RotaTeq®. Screening for maternally acquired HIV infection can often be done by the time of RV vaccination at 6–8 weeks of age, but the result is not needed for decision-making on RV vaccination.

11.12.3 Immunodeficiency

The RV vaccine causes symptomatic disease (prolonged diarrhea and viral shedding) in children with severe combined immunodeficiency, and therefore vaccination is contraindicated and exposure to RV vaccine shedders should be avoided in such children. Other immunodeficiencies may be regarded similarly. Selective IgA deficiency may result in the prolonged shedding of the RV vaccine, but does not constitute a safety problem and, in any case, is usually not diagnosed by the time of RV vaccination.

11.12.4 Short Gut Syndrome and Intestinal Failure

The RV vaccine may cause substantial symptoms in children with short bowel, but given the severity of the wild-type RV infection, they should nevertheless be vaccinated under close observation.

11.13 Non-live RV Vaccines

The need and rationale for the development of non-live RV vaccines as alternatives to live oral RV vaccines are based on efficacy and safety concerns. IS remains a serious safety concern, although the magnitude of the problem is regarded as tolerable. Also, the possibility of contamination by adventitious agents such as PCV is associated with live vaccines. As for efficacy, all live RV vaccines have shown a relatively (in comparison with developed countries) low efficacy in developing countries for reasons that may not be easily remedied. Parenteral immunization may induce a higher level of protection against RV disease bypassing the intestinal obstacles.

The most advanced non-live RV vaccine is trivalent subunit P2-VP8 vaccine, originated

from NIH and endorsed by PATH. This vaccine contains VP8 proteins from rotavirus P-types P(4), P(6), and P(8). The vaccine has been tested against challenge by Rotarix vaccine and has now progressed to an efficacy trial in Africa.

A most straightforward approach is development of inactivated whole virion RV vaccine (IRV). There are several investigative IRVs in the pipeline.

Rotavirus VLP vaccines have been tested over the years preclinically. The simplest one is VP6 alone.

In addition, VLP vaccines may contain RV structural proteins VP2, VP4, and VP7, to eventually form VP2/4/6/7 VLPs. None have been tested in humans as yet.

Rotavirus VP6 alone forms tubular structures or spheres under appropriate conditions, and particulate forms of VP6 are strong immunogens. VP6 is also the simplest possible RV candidate vaccine consisting of only a single protein, which is considered a group antigen common to all group A rotaviruses. A whole new scenario might be a combined immunization against RV and norovirus GE using a RV VP6–norovirus VLP vaccine (see ▶ Chap. 25).

Further Reading

Bishop RF, Davidson GP, Holmes IH, Ruck BJ. Virus particles in epithelial cells of duodenal mucosa from children with acute non-bacterial gastroenteritis. Lancet. 1973;2(7841):1281–3.

Blazevic V, Lappalainen S, Nurminen K, Huhti L, Vesikari T. Norovirus VLPs and rotavirus VP6 protein as combined vaccine for childhood gastroenteritis. Vaccine. 2011;29:8126–33.

Braeckman T, Van Herck K, Meyer N, RotaBel Study Group, et al. Effectiveness of rotavirus vaccination in prevention of hospital admissions for rotavirus gastroenteritis among young children in Belgium: case-control study. BMJ. 2012;345:e4752.

Dornbusch H-J, Vesikari T, Guarino A, LoVecchio A, Koletzko B. Should rotavirus vaccination be offered to all children in Europe, or only subgroups of children with assumed increased risk? Eur J Pediatr 2020;179:1489−93.

Hemming M, Räsänen S, Huhti L, Paloniemi M, Salminen M, Vesikari T. Major reduction of rotavirus, but not norovirus, gastroenteritis in children seen in hospital after the introduction of RotaTeq vaccine into the National Immunization Programme in Finland. Eur J Pediatr. 2013;172(6):739–46.

https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Rotarix/pdf/ROTARIX-PI-PIL.PDF.

http://www.merck.com/product/usa/pi_circulars/r/rotateq/rotateq_pi.pdf.

Hemming-Harlo M, Lähdeaho M-L, Mäki M, Vesikari T. Rotavirus vaccination does not increase type 1 diabetes and may decrease celiac disease in children and adolescents. PIDJ 2019;38:539−541.

Joensuu J, Koskenniemi E, Pang XL, Vesikari T. Randomised placebo-controlled trial of rhesus-human reassortant rotavirus vaccine for prevention of severe rotavirus gastroenteritis. Lancet. 1997;350(9086):1205–9.

Libster R, McNeal M, Walter EB, et al. Safety and immunogenicity of sequential rotavirus vaccine schedules. Pediatrics. 2016;137(2):e20152603.

Markkula J, Hemmingharlo M, Savolainen-Kopra C, Al-Hello H, Vesikari T. Continuing rotavirus circulation in children and adults despite high coverage rotavirus vaccination in Finland. J Infection 2020;80:76-83.

Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA, Zanardi LR, Setia S, Fair E, LeBaron CW, Wharton M, Livengood JR, Rotavirus Intussusception Investigation Team. Intussusception among infants given an oral rotavirus vaccine. N Engl J Med. 2001;344(8):564–72.

Payne DC, Boom JA, Staat MA, et al. Effectiveness of pentavalent and monovalent rotavirus vaccines in concurrent use among US children <5 years of age, 2009–2011. Clin Infect Dis. 2013;57(1):13–20.

Rivero-Calle I, Comez-Roal J, Martinon-Torres F. Systemic features rotavirus infection. J Infect 2016;5:98−105.

Rogers MM, Besu T, Kim C. Lower incidence rate of type 1 diabetes after receipt of the rotavirus vaccine in the United States, 2001-2017. Sci Rep 2019;9:7727.

Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med. 2006;354(1):11–22.

Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes. Scand J Infect Dis. 1990;22(3):259–67.

Simonsen L, Viboud C, Elixhauser A, Taylor RJ, Kapikian AZ. More on RotaShield and intussusception: the role of age at the time of vaccination. J Infect Dis. 2005;192(Suppl 1):S36–43.

Soriano-Gabarro M, Mrukowicz J, Vesikari T, Verstraeten T. Burden of rotavirus disease in European Union countries. Pediatr Infect Dis J. 2006;25(Suppl):7–11.

Svensson L, Sheshberadaran H, Vesikari T, Norrby E, Wadell G. Immune response to rotavirus polypeptides after vaccination with heterologous rotavirus vaccines (RIT 4237, RRV-1). J Gen Virol. 1987;68(Pt 7):1993–9.

Velazquez FR, Matson DO, Calva JJ, Guerrero L, Morrow AL, Carter-Campbell S, et al. Rotavirus infections in infants as protection against subsequent infections. N Engl J Med. 1996;335(14):1022–8.

Vesikari T, Isolauri E, D'Hondt E, Delem A, André FE, Zissis G. Protection of infants against rotavirus diarrhoea by RIT 4237 attenuated bovine rotavirus strain vaccine. Lancet. 1984;1:977–81.

Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med. 2006;354:23–33.

Vesikari T, Itzler R, Karvonen A, Korhonen T, Van Damme P, Behre U, Bona G, Gothefors L, Heaton PM, Dallas M, Goveia MG. RotaTeq, a pentavalent rotavirus vaccine: efficacy and safety among infants in Europe. Vaccine. 2009;28(2):345–51.

Vesikari T, Van Damme P, Giaquinto C, Dagan R, Guarino A, Szajewska H, Usonis V. European Society for Paediatric Infectious Diseases consensus recommendations for rotavirus vaccination in Europe: update 2014. Pediatr Infect Dis J. 2015;34:635–43.

WHO position paper. Rotavirus vaccines. Wkly Epidemiol Rec. 2013;88:49–64.

Hepatitis A Vaccines

Pierre Van Damme and Greet Hendrickx

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_12

12.1 The Disease

Hepatitis A is a liver disease caused by the hepatitis A virus (HAV). The incubation period of hepatitis A is usually 14–28 days. Symptoms of hepatitis A range from mild to severe and can include fever, malaise, loss of appetite, diarrhea, nausea, abdominal discomfort, dark-colored urine, and jaundice (a yellowing of the skin and whites of the eyes). Infected children under 6 years of age do not usually experience noticeable symptoms, and only 10% develop jaundice. Among older children and adults, infection usually causes more severe symptoms, with jaundice occurring in more than 70% of cases. Because of the often asymptomatic or subclinical course of hepatitis A infection, incidence rates are often underestimated. Review data from 1990 to 2005 suggest a global increase from 117 million HAV infections in 1990 to 121 million infections in 2005.

Hepatitis A sometimes relapses. The person who just recovered falls sick again with another acute episode. This is, however, followed by recovery. Unlike hepatitis B and C, hepatitis A infection does not cause chronic liver disease and is rarely fatal.

The estimated case–fatality ratio of hepatitis A varies with age and ranges from 0.1% among children <15 years of age to 0.3% among persons 15–39 years of age and is 2.1% among adults aged ≥40 years. In Argentina, 0.4% of pediatric patients developed fulminant hepatitis, 60% of which were fatal. Reports from South America and the Republic of Korea have raised concerns that the incidence of fulminant hepatitis A might be rising, particularly in children.

There is no specific treatment for hepatitis A. Recovery from symptoms following infection may be slow and may take several weeks or months.

12.2 Epidemiology

Hepatitis A occurs sporadically and in epidemics worldwide, with a tendency toward cyclic recurrences. The hepatitis A virus is one of the most frequent causes of foodborne infection. The HAV persists in the environment and can withstand food production processes routinely used to inactivate and/or control bacterial pathogens.

The HAV is transmitted primarily via the fecal–oral route, that is, when an uninfected person ingests food or water that has been contaminated with the feces of an infected person. In families, this may happen when an infected person prepares food for family members with dirty hands. Waterborne outbreaks, though infrequent, are usually associated with sewage-contaminated or inadequately treated water. The virus can also be transmitted through close physical contact with an infectious person, although casual contact among people does not spread the virus.

In developing countries with poor sanitary conditions and hygienic practices, most children (90%) are infected with the HAV before the age of 10 years, mostly with no noticeable symptoms. Epidemics are uncommon because older children and adults are generally immune. Symptomatic disease rates in these areas are low and outbreaks are rare.

In middle-income countries, often developing countries with transitional economies, and regions where sanitary conditions are variable, children often escape infection in early childhood and reach adolescence or adulthood without immunity. Ironically, these improved economic and sanitary conditions may lead to accumulation of adolescence and adults who have never been infected and who have no immunity. This higher susceptibility in older age groups may lead to higher disease rates, and large outbreaks can occur in these communities.

In industrialized countries with good sanitary and hygienic conditions, infection rates are low. Disease may occur among adolescents and adults in high-risk groups, such as injecting drug users, men who have sex with men (MSM), people travelling to areas of high endemicity, and isolated populations, such as closed communities. Seroprevalence and surveillance in Europe illustrate the large variability in hepatitis A endemicity across the WHO-EURO region, ranging from very

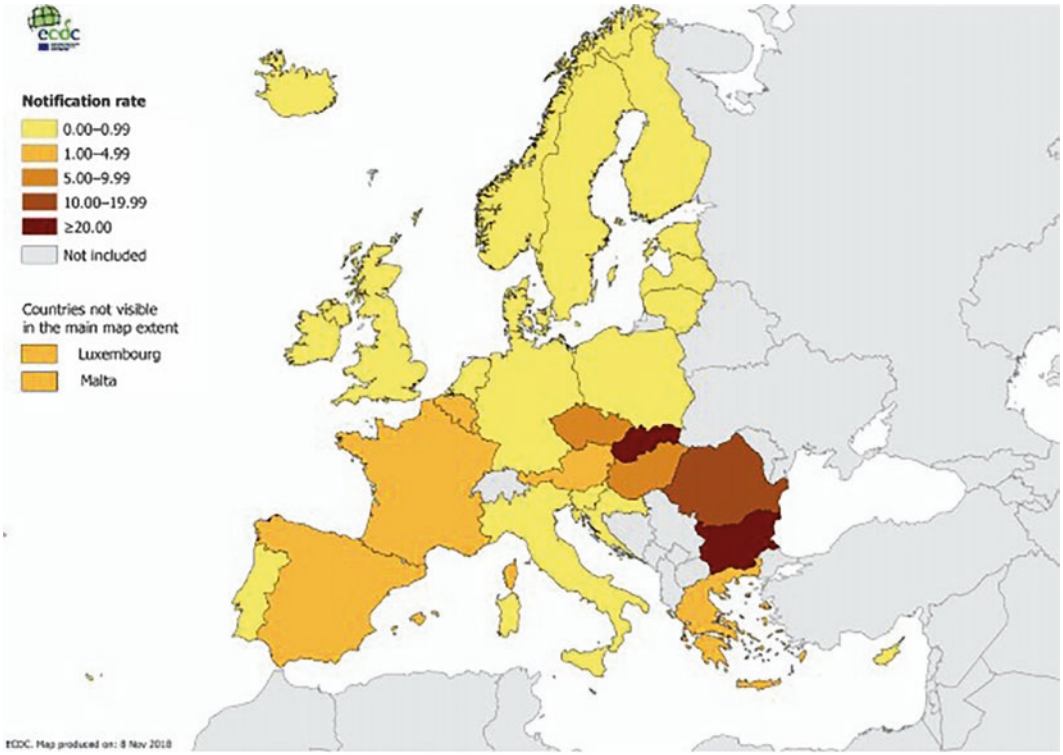


Fig. 12.1 Distribution of confirmed hepatitis A cases per 100,000 population by country in EU/EEA countries, 2016 (► https://www.ecdc.europa.eu/sites/default/files/documents/AER-2016-hepatitis-A.pdf)

low in Scandinavian countries (15%) and low in Western Europe (reaching 40–70% somewhere between 35 and 70 years) to intermediate and high in Central Europe and the Newly Independent States[1] (with 50% seropositivity reached during childhood or by the age of 20). Data from 2005 show a further overall trend of decreasing incidence, with seroprevalence rates in Europe still increasing from west to east. ECDC data based on notification from 1997 to 2011 mention a decrease from 10.0 to 2.5/100,000 population, with 21 of the 28 countries reporting rates less than or equal to 1/100,000. Since the end of 2016, several EU countries have been reporting an increase of hepatitis A cases, both in the general population and in specific risk groups, predominantly in men who have sex with men. Since the beginning of 2017, 14 countries, i.e., Austria, the Czech Republic, Denmark, Finland, France, Germany, Ireland, Latvia, Lithuania, the Netherlands, Poland, Portugal, Slovenia, and Spain, reported 5983 cases of hepatitis A according to online publicly available information (Fig. 12.1). This is higher than the average annual number of cases reported by this group of countries to The European Surveillance System (TESSy) between 2007 and 2016 (2506 cases).

1 Newly Independent States (NIS): The NIS is a collective reference to 12 republics of the former Soviet Union: Russia, Ukraine, Belarus (formerly Byelorussia), Moldova (formerly Moldavia), Armenia, Azerbaijan, Uzbekistan, Turkmenistan, Tajikistan, Kazakhstan, Kirgizstan (formerly Kirghizia), and Georgia. Following dissolution of the Soviet Union, the distinction between the NIS and the Commonwealth of Independent States (CIS) was that Georgia was not a member of the CIS. That distinction dissolved when Georgia joined the CIS in November 1993.

12.3 Prevention

Improved sanitation, food safety, and immunization are the most effective ways of combating hepatitis A. The spread of hepatitis A can be reduced by adequate supplies of safe drinking water; proper disposal of sewage within communities; and personal hygiene practices such as regular hand-washing with safe water.

12.4 HAV Vaccines

Several inactivated and live attenuated vaccines against hepatitis A were developed in the 1980s and licensed for use in the early 1990s. These vaccines are safe and well-tolerated, they are highly immunogenic, and they provide long-lasting protection against hepatitis A disease in children and adults. Four formalin-inactivated, cell culture-produced, whole-virus vaccines have been available internationally: Havrix (HM 175 strain, GlaxoSmithKline Biologicals, Rixensart, Belgium), Vaqta (CR326F strain, Merck, West Point, PA, USA), Epaxal (RG SB strain, Crucell [Janssen vaccines], Leiden, Netherlands), and Avaxim (GBM strain, Sanofi Pasteur, Lyon, France) are licensed in most parts of the world. Epaxal is no longer available.

Other hepatitis A vaccines are produced with limited or local distribution. These include, for instance, a Chinese live attenuated vaccine, MEVAC™-A (H2 strain, Zhejiang Academy of Medical Sciences, Hangzhou, People's Republic of China), and a vaccine manufactured by Vaccine and Bio-product Company in Vietnam since 2004.

Several types of combination vaccines containing an inactivated hepatitis A vaccine have been developed to protect individuals against more than one infectious disease when travelling to endemic countries. Such vaccines include Twinrix (GlaxoSmithKline Biologicals, Rixensart, Belgium), the only combined vaccine against both hepatitis A and hepatitis B infections, licensed since 1996; other combined vaccines include Hepatyrix (GlaxoSmithKline Biologicals, Rixensart, Belgium) and ViATIM (Sanofi Pasteur, Lyon, France), both protecting against hepatitis A and typhoid fever.

Table 12.1 Dosage and schedule for inactivated monovalent hepatitis A vaccines (in chronological order)

Vaccine	Antigen content (HAV strain)	Volume (ml)	Two-dose schedule (months)
Havrix™720 Junior	720 El.U (HM 175)	0.5	0, 6–12
Havrix™1440 Adult	1440 El.U (HM 175)	1	0, 6–12
Vaqta®	25 U (CR326 F)	0.5	0, 6–18
Vaqta®	50 U (CR326 F)	1	0, 6–18
Avaxim® 80 U Pediatric	80 antigen units (GBM)	0.5	0, 6–12
Avaxim ®160 U	160 antigen units (GBM)	0.5	0, 6–12

HAV hepatitis A virus, *El. U* ELISA units

Inactivated hepatitis A vaccines all contain HAV antigen, but the content per vaccine dose is expressed in different units by various manufacturers (Table 12.1). Recommended vaccination schedules, ages for which the vaccine is licensed, and whether there is a pediatric and adult formulation also vary. All vaccines are licensed from 1 year of age in most countries. The inactivated vaccines are produced according to similar manufacturing processes involving whole-virus preparations of HAV strains growing in human MRC-5 diploid cell cultures, with subsequent virus purification and inactivation with formalde-

hyde. Havrix (HM175 strain), Vaqta (CR326F strain), and Avaxim (GBM strain) are adjuvanted with alum, whereas Epaxal (RG SB strain) contained a liposome adjuvant in the form of immunopotentiating reconstituted influenza virosomes (IRIV). Havrix and Avaxim contain 2-phenoxyethanol as a preservative, whereas the other vaccines are preservative-free formulations. All vaccines are administered via intramuscular injection, according to varying dosages and schedules, as described in ◘ Table 12.1.

If medically indicated, such as in hemophiliacs or in patients under anticoagulation, all four vaccines can be given subcutaneously.

12.5 Vaccine Tolerability

To date, millions of doses of hepatitis A vaccines have been administered to children and adults worldwide, with no serious adverse event ever statistically linked to their use. The safety profile of inactivated hepatitis A vaccines has been extensively reviewed, and results from clinical trials, and those from post-marketing surveillance studies, have demonstrated that the vaccines are all safe and well-tolerated. The most commonly reported adverse events included mild and transient local site reactions, such as pain, swelling, and redness (21% in children and 52% in adults). General reactions such as low fever, fatigue, diarrhea, vomiting, and headache were reported in less than 5% of subjects.

12.6 Vaccine Immunogenicity and Protective Efficacy

The absolute minimum level of HAV antibodies required to prevent HAV infection has not been defined. Experimental studies in chimpanzees have shown that low levels of passively transferred antibody (<10 mIU/mL) obtained from vaccinated persons do not protect against infection, but do prevent clinical hepatitis and virus shedding. In the absence of an absolute lowest protective level of antibody required to prevent HAV infection, the lower limit of detection of the specific assay used in a study is generally considered as an accepted correlate of protection, i.e., 20 mIU/ml or 33 mIU/ml by ELISA in clinical studies with Havrix, 20 mIU/ml for Avaxim and Epaxal, and 10 mIU/ml for Vaqta.

Currently licensed inactivated hepatitis A vaccines have proven highly immunogenic in extensive clinical studies, conferring protective immunity against the disease 2–4 weeks after administration of the first dose. Recent data have shown that most individuals seroconvert within 2–4 weeks of vaccination, with rates ranging from 95 to 100% in children and adults. Administration of the second dose of the primary schedule (6–18 months after the first dose) ensures long-term protection. Review of the immunogenicity data for each vaccine and results from several comparative clinical trials demonstrate the equally high immunogenicity and interchangeability of hepatitis A vaccines.

The protective efficacy of inactivated hepatitis A vaccines against clinical disease has been documented in several controlled clinical efficacy trials. The cumulative protective efficacy of the vaccination course with Havrix in more than 40,000 Thai children aged 1–16 years was 95%. The observed protective efficacy of Vaqta was 100% after one vaccine dose in a trial involving more than 1000 children aged 2–16 years from a highly endemic community in the USA. In a trial involving 274 Nicaraguan children aged 1.5–6 years, the protective efficacy of a single dose of Epaxal was also 100%.

The presence of passively transferred antibodies from previous maternal HAV infection has been shown to result in reduced antibody response to hepatitis A vaccination in infants. However, in spite of lower antibody concentrations observed after primary vaccination of infants born to anti-HAV seropositive mothers, several studies have indicated that priming and immune memory were induced, as demonstrated by the anamnestic response at the time of the booster. This was the case after a second vaccine dose administered at 12 months to 300 infants born to either anti-HAV seronegative or seropositive mothers in a study conducted in Israel. Similarly, in a study conducted in Turkey with children who had received pri-

mary vaccination at 2, 4, and 6 months of age, all subjects showed anamnestic response after booster vaccination at 4 years of age. At 15 months of age, protective levels of antibody were also present in 93% of American Indian infants born to anti-HAV-positive mothers, who had received primary immunization at 2, 4, and 6 months or at 8 and 10 months of age.

12.7 Co-administration

Such findings relating to hepatitis A vaccine immunogenicity in children younger than 2 years of age, in addition to studies showing that hepatitis A vaccine may be effectively and safely co-administered with other pediatric vaccines, such as diphtheria–tetanus–acellular pertussis, inactivated and oral polio, *Haemophilus influenzae* type b, and hepatitis B vaccines, are of particular importance in the implementation of prevention strategies involving routine childhood vaccination programs. Other studies in adults have demonstrated effective and safe co-administration of hepatitis A vaccine with traveler vaccines, including hepatitis B, polio, diphtheria, tetanus, typhoid fever, yellow fever, rabies, cholera, and Japanese encephalitis.

12.8 Flexibility of Schedule

Hepatitis A vaccine has a recommended two-dose schedule, with the second dose being administered at 6–12 months in the case of Havrix, Avaxim, and Epaxal, and at 6–18 months in the case of Vaqta. However, timing of the second dose is flexible since an anamnestic response has been shown to be triggered by a second dose when administered several years after the first vaccine dose in children and adults. Flexible two-dose vaccination schedules with a "delayed" second dose are of critical importance because travelers often miss the second dose and present some years later with a new/repeated indication for hepatitis A vaccination. In addition, a flexible schedule may help to introduce hepatitis A vaccines into established childhood routine vaccination programs. For example, a vaccination schedule for infants/children with the first dose administered during the second year of life and a second dose given at school entry at the age of 5–6 seems worth investigating. Also, additional long-term follow-up studies of individuals who have received a single vaccine dose help in formulating future recommendations in terms of dosing schedule: a systematic review of published data from 2000 till 2019 to assess evidence for one-dose and two-dose universal hepatitis A vaccination in children shows rapid and persistent decline in hepatitis A incidence, with vaccine effectiveness above 95%. Because evidence is limited for one-dose universal vaccination programs, long-term monitoring of one-dose programs is essential.

12.9 Early Protection and Duration of Protection

Hepatitis A vaccines confer early protection, as confirmed by recent data showing that most individuals seroconvert within 2 weeks of vaccination, well within the 28-day incubation period of the virus. Travelers receiving the vaccine any time before departure may thus be expected to be protected against the disease.

With regard to the duration of immunity, long-term follow-up studies have shown persistence of protective anti-HAV antibodies for at least 20 years in children, adolescents, and adults, post-vaccination. Mathematical models using data from vaccinated adults have estimated protective antibodies to persist for at least 25–50 years in 99.4% of vaccinees.

12.10 Field Effectiveness of Routine Vaccination Programs

Hepatitis A routine immunization of young children has proven effective in rapidly reducing disease incidence and maintaining very low incidence levels among vaccine recipients and across all other age groups, thus demonstrating the development of herd immunity, in a number of settings. A national toddler immunization pro-

gram in place in Israel since 1999 has also demonstrated vaccine effectiveness, with a decrease in the annual incidence rate of hepatitis A disease from 50.4 per 100,000 (1993–1998) to 2.2–2.5 per 100,000 (2002–2004), representing more than a 95% reduction. This marked decline was seen in targeted vaccine recipients (85–90% coverage), and in all other age groups, thus demonstrating the effectiveness of hepatitis A vaccination and the development of herd immunity. Mass vaccination programs also proved effective in localized regions of intermediate to high HAV endemicity of industrialized nations with otherwise low endemicity levels, such as the Puglia region of Italy, the Catalonia region of Spain, and North Queensland, Australia.

In 2005, public health authorities in Argentina began a universal immunization program in 12-month-old children based on a single-dose schedule of inactivated HAV vaccine. In 2007, with vaccination coverage of 95%, the incidence of symptomatic viral hepatitis A had dropped by >80% in all age groups. Six years after implementation of this country-wide single-dose program, no hepatitis A cases have been detected among vaccinated individuals, whereas among the unvaccinated a number of cases have occurred, confirming continued circulation of HAV in the Argentinian population. An increasing number of countries in Latin America are currently implementing such a one-dose schedule.

12.11 Field Effectiveness of Post-exposure Administration and in an Outbreak Control Situation

Studies in chimpanzees, further supported by randomized trials in humans, have shown that hepatitis A vaccine is effective in preventing HAV infection when administered post-exposure. The post-exposure window for successful vaccination has been defined as the period within 2 weeks of exposure; there is indeed increasing evidence for the efficacy of hepatitis A vaccine as a valid alternative to passive post-exposure prophylaxis with immune globulin (no longer available in most countries), allowing, in particular, for a better control of outbreak situations. Results from studies conducted in chimpanzees have also shown that vaccinated animals did not shed HAV once exposed to the wild-type virus, thus demonstrating that the use of vaccines is effective at controlling the spread in the case of outbreak.

The effectiveness of hepatitis A vaccination to control outbreak situations has been reported in various settings in the USA, including rural communities from Alaska, and Europe, including Slovakia, Croatia, the UK, and Italy.

12.12 Immunization Programs

12.12.1 Risk Group Approach

Based on the transmission of HAV, several risk groups have been identified, for whom prevention by vaccination is recommended by official institutions such as the World Health Organization (WHO), the Advisory Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention, and the Viral Hepatitis Prevention Board. These risk groups can either be at increased risk for HAV infection (e.g., travelers to endemic regions) or have a higher probability of developing severe complications if a HAV infection were to occur (e.g., chronic liver disease patients; see ► Box 12.1).

Box 12.1 Summary of Current ACIP, WHO, and VHPB Recommendations for Hepatitis A Vaccination

Persons at increased risk for HAV who should be routinely vaccinated:

- Persons travelling to or working in countries that have high or intermediate endemicity of infection.
- MSM.
- Intravenous drug users.
- Persons who have an occupational risk for infection.
- Persons who have clotting factor disorders.
- Day-care center children and staff.
- Persons in residential institutions.
- Food handlers.
- Healthcare workers.

Vaccination of persons who have chronic liver disease:

- Susceptible persons who have chronic liver disease or who are either awaiting or have received liver transplants should be vaccinated.

Hepatitis A vaccination during outbreaks:

- Vaccination for outbreak control should take into consideration the characteristics of hepatitis A epidemiology in the community and existing hepatitis A vaccination programs.

Sources: CDC US, World Health Organization, Viral Hepatitis Prevention Board.

12.13 Universal Immunization Programs

Vaccination against hepatitis A should be part of a comprehensive plan for the prevention and control of viral hepatitis. Planning for large-scale immunization programs should involve careful economic evaluations and consider alternative or additional prevention methods, such as improved sanitation, and health education for improved hygiene practices.

Whether to include the vaccine in routine childhood immunizations depends on the local context. The proportion of susceptible people in the population and the level of exposure to the virus should be considered. Generally speaking, countries with intermediate endemicity benefit the most from the universal immunization of children. Countries with low endemicity may consider vaccinating high-risk adults. In countries with high endemicity, the use of vaccine is limited as most adults are naturally immune.

As of 2019, at least 20 countries used hepatitis A vaccine in the routine immunization of children nationally including 6 countries with a single-dose program (Argentina, Brazil, Chile, Colombia, Paraguay, and Turkmenistan).

In the WHO-EURO region, Israel started a nationwide universal vaccination program in 1999, thereby offering two doses of HAV vaccine to toddlers at 18 and 24–30 months of age, with coverage rates reaching 85–90%. Italy (Puglia) and Spain (Catalonia) have regional universal HAV vaccination programs. In Puglia, Italy, the HAV vaccine has been offered to children aged 15–18 months since 1997, and the existing hepatitis B vaccination program for 12-year-old adolescents simultaneously started using the combined vaccine against hepatitis A and B; in Catalonia, Spain, 12-year-old adolescents have also been offered the combined hepatitis A and B vaccine since 1998–1999. In addition, Greece and Turkey recently introduced a universal immunization program in toddlers.

Regarding immunization for outbreak response, recommendations for hepatitis A vaccination should also be site-specific. The feasibility of rapidly implementing a widespread immunization campaign needs to be included. Vaccination to control community-wide outbreaks is most successful in small communities, when the campaign is started early and when high coverage of multiple age groups is achieved. Vaccination efforts should be supplemented by health education to improve sanitation, hygiene practices, and food safety.

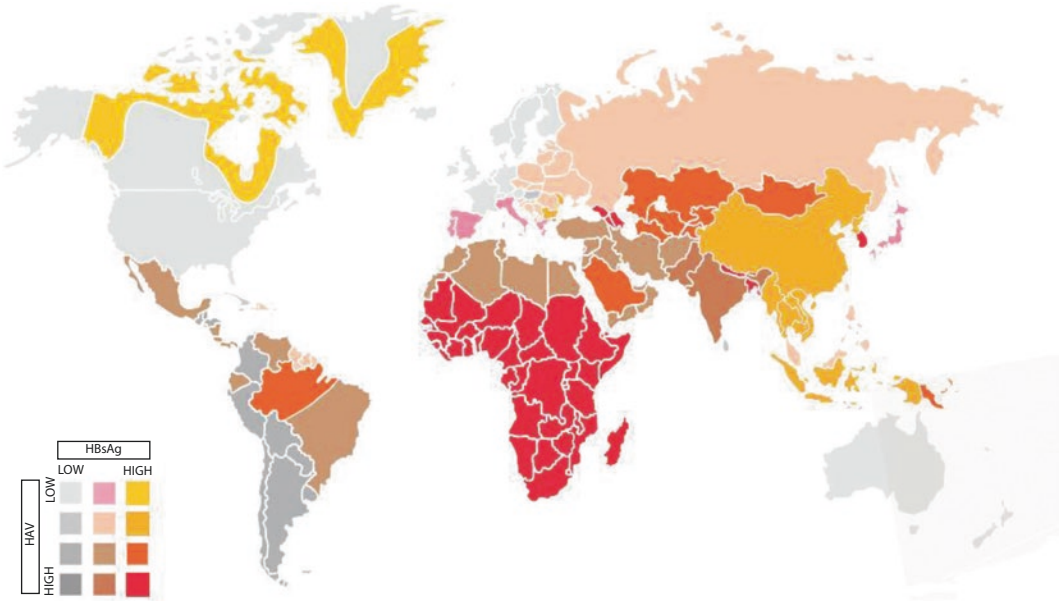


Fig. 12.2 Combined map of hepatitis B surface antigen (HBsAg; date not specified) and estimated prevalence of hepatitis A virus (HAV; 2005). (Adapted from Jacobsen and Wiersma 2010; Plotkin and Orenstein 2013)

12.14 Combined Hepatitis a and B Vaccine

Infections caused by the HAV and hepatitis B virus (HBV), which occur across the globe, are associated with significant morbidity and mortality and inflict a considerable healthcare burden (Fig. 12.2). Vaccination is the most effective method of conferring long-term protection against both viruses and, together with improved sanitation and hygiene, has resulted in a steady reduction in global infection.

Monovalent vaccines against hepatitis A and B are immunogenic and well-tolerated with long-term immunogenic benefits observed in clinical studies with up to 20 years' follow-up. Because of the considerable overlap of risk factors and areas of high endemicity for both diseases, a combined vaccine against both viruses represents a pragmatic approach that reduces the number of vaccine administrations, in particular for travelers, patients with chronic liver disease, patients infected with HCV, or persons at increased risk of sexually transmitted infections (e.g., MSM).

Table 12.2 Three presentations of combined vaccine against hepatitis A and B

Vaccine	Target population	Formulation	Schedule
Twinrix	Adults	1.0 ml–720 El.U HAV–20 µg HBsAg	3 doses
Twinrix pediatric	Children (1–11 years)	0.5 ml–360 El.U HAV–10 µg HBsAg	3 doses
Ambirix	Children and adolescents (1–15 years)	1.0 ml–720 El.U HAV–20 µg HBsAg	2 doses

HBsAg surface antigen of the hepatitis B virus

Three presentations of the combined vaccine against hepatitis A and B are available (Twinrix, Twinrix Pediatric, and Ambirix; GSK Vaccines, Belgium; Table 12.2). These bivalent vaccines are widely available, with a safety and immunogenicity profile demon-

strated as being comparable with that of the respective monovalent vaccines alone. These vaccines confer concurrent protection against the two infections while reducing the number of injections, associated costs, and other logistic issues, offering greater convenience to the vaccinee and healthcare provider.

After complete vaccination with these combined hepatitis A and B vaccines, the rate of anti-HAV seropositivity ranged from 96% to 100% in adults, children, and adolescents. The rate of hepatitis B surface antibody (anti-HBs) ranged from 82% to 100%, with decreasing immunogenicity response with increasing age. Immunogenicity results were equal to or higher for both anti-HAV and anti-HBs following Twinrix and Ambirix vaccination compared with monovalent hepatitis A and B vaccination. Long-term kinetics of the combined vaccine-induced hepatitis A and B antibodies perfectly mimics what was respectively demonstrated with the monovalent hepatitis A and B vaccines, both in terms of long-term persistence of vaccine-induced antibodies (at least 20 years shown in the adult population) and immune memory: the latter was demonstrated by mounting a strong anamnestic response after a challenge dose of HAV or HBV vaccine, indicative of the induction and persistence of immune memory.

Co-administration of Twinrix pediatric or Ambirix with other routine childhood vaccines was immunologically non-inferior to administration of the combined hepatitis A and B vaccine alone and did not significantly alter the safety profile. Safety profiles of the combined versus monovalent hepatitis A and B vaccines were similar.

Further Reading

Andani A, Van Damme P, Bunge EM, Salgado F, van Hoorn RC, Hoet B. One or two doses of hepatitis A vaccine in universal immunization programs in children in 2020: a systematic review. Vaccine. 2021 Jan 29:S0264-410X(21)00054-2. https://doi.org/10.1016/j.vaccine.2021.01.038.

André F, Van Damme P, Safary A, Banatvala J. Inactivated Hepatitis A vaccine: immunogenicity, efficacy, safety and review of official recommendations for use. Expert Rev Vaccines. 2002;1(1):9–23.

Bakker M, Bunge E, Marano C, de Ridder M, De Moerlooze L. Immunogenicity, effectiveness and safety of combined hepatitis A and B vaccine: a systematic literature review. Expert Rev Vaccines. 2016;15:829–51.

Bell BP, Feinstone SM. Hepatitis A vaccine. In: Plotkin SA, Orenstein WA, editors. Vaccines. 4th ed. Philadelphia: Saunders; 2004. p. 269–97.

Beran J, Beutels M, Levie K, Van Damme P, Dieussaert I, Gillet M, et al. A single dose, combined vaccine against typhoid fever and hepatitis A: consistency, immunogenicity and reactogenicity. J Travel Med. 2001;7(5):246–52.

Dagan R, Amir J, Mijalovsky A, Kalmanovitch I, Bar-Yochai A, Thoelen S, et al. Immunization against hepatitis A in the first year of life: priming despite the presence of maternal antibody. Pediatr Infect Dis J. 2000;19:1045–52.

Dagan R, Leventhal A, Anis E, Slater P, Ashur Y, Shouval D. Incidence of hepatitis A in Israel following Universal Immunization of Toddlers. JAMA. 2005;294:202–10.

Gossner CM, et al. Changing hepatitis A epidemiology in the European Union: new challenges and opportunities. Eurosurveillance. 2015;20(16):1–6.

Herzog C, Van Herck K, Van Damme P. Hepatitis A vaccination and its immunological and epidemiological long-term effects – a review of the evidence. Human Vaccines & Immunotherapeutics 2020; 16: 1−24. https://doi.org/10.1080/21645515.2020.1819742

Innis BL, Snitbhan R, Kunasol P, Laorakpongse T, Poopatanakool W, Kozik CA, et al. Protection against hepatitis A by an inactivated vaccine. JAMA. 1994;271:1328–34.

Jacobsen KH, Koopman JS. Declining hepatitis A seroprevalence: a global review and analysis. Epidemiol Infect. 2004;132:1005–22.

Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine. 2010;28:6653–7.

Letson GW, Shapiro CN, Kuehn D, Gardea C, Welty TK, Krause DS, et al. Effect of maternal antibody on immunogenicity of hepatitis A vaccine in infants. J Pediatr. 2004;144:327–32.

Loutan L, Bovier P, Althaus B, Glück R. Inactivated virosome hepatitis A vaccine. Lancet. 1994;343:322–34.

Mayorga O, Bühler S, Jaeger VK, Bally S, Hatz C, Frösner G, Protzer U, Van Damme P, Egger M, Herzog C. Single-dose Hepatitis A immunization: 7.5-year observational pilot study in Nicaraguan children to assess protective effectiveness and humoral immune memory response. J Infect Dis. 2016;214(10):1498–506.

Martin JC, Petrecz ML, Stek JE, Simon JK, Goveia MG, Klopfer SO. Using the power law model to predict the long-term persistence and duration of detectable hepatitis A antibody after receipt of hepatitis A vaccine (VAQTA™). Vaccine. 2021 Apr 15:S0264-

410X(21)00345-5. https://doi.org/10.1016/j.vaccine.2021.03.052.

Ott JJ, Wiersma ST. Single-dose administration of inactivated hepatitis A vaccination in the context of hepatitis A vaccine recommendations. Int J Infect Dis. 2013;17(11):e939–44. https://doi.org/10.1016/j.ijid.2013.04.012. Review.

Ott JJ, Irving G, Wiersma ST. Long-term protective effects of hepatitis A vaccines. A systematic review. Vaccine. 2012;31(1):3–11. https://doi.org/10.1016/j.vaccine.2012.04.104. Review.

Plotkin S,Orenstein W, Offit P. Vaccines. 6th (ed). 2013 Saunders. ISBN: 9781455737987. https://www.elsevier.com/books/vaccines/plotkin/978-1-4557-0090-5

Stuurman AL, Marano C, Bunge EM, De Moerlooze L, Shouval D. Impact of universal mass vaccination with monovalent inactivated hepatitis A vaccines – a systematic review. Human Vaccines & Immunotherapeutics 2017; 13 (3): 724−736

Theeten H, Van Herck K, Van Der Meeren O, Crasta P, Van Damme P, Hens N. Long-term antibody persistence after vaccination with a 2-dose Havrix (inactivated hepatitis A vaccine): 20 years of observed data, and long-term model-based predictions. Vaccine. 2015;33(42):5723–7. https://doi.org/10.1016/j.vaccine.2015.07.008.

Van Damme P, Van Herck K. A review of the efficacy, immunogenicity and tolerability of a combined hepatitis A and B vaccine. Expert Rev Vaccines. 2004;3(3):249–67.

Van Damme P, Van Herck K. Effect of hepatitis A vaccination programs. JAMA. 2005;294:246–8.

Van Damme P, Thoelen S, Cramm M, De Groote K, Safary A, Meheus A. Inactivated hepatitis A vaccine: reactogenicity, immunogenicity, and long-term antibody persistence. J Virol Med. 1994;44(4):446–51.

Van Damme P, Banatvala J, Fay O, Iwarson S, McMahon B, Van Herck K, et al. Consensus statement: hepatitis A booster vaccination: is there a need? Lancet. 2003;362:1065–71.

Van Damme P, Leroux-Roels G, Suryakiran P, Folschweiller N, Van Der Meeren O. Persistence of antibodies 20 y after vaccination with a combined hepatitis A and B vaccine. Hum Vaccin Immunother. 2017;13:972–80.

Vidor E, Dumas R, Porteret V, Bailleux F, Veitch K. Aventis Pasteur vaccines containing inactivated hepatitis A virus: a compilation of immunogenicity data. Eur J Clin Microbiol Infect Dis. 2004;23(4):300–9.

Wasley A, Samandari T, Bell B. Incidence of hepatitis A in the United States in the era of vaccination. JAMA. 2005;294:194–201.

Werzberger A, Mensch B, Kuter B, Brown L, Lewis J, Sitrin R, et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. N Engl J Med. 1992;327(7):453–7.

World Health Organization. Hepatitis A vaccines WHO position paper. Weekly Epidemiology Record. 2012;875:261–76. https://www.who.int/wer/2012/wer8728_29.pdf?ua=1

Hepatitis B Vaccines

Pierre Van Damme and Alex Vorsters

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_13

13.1 The Disease

Hepatitis B virus, previously called the Dane particle, is a 42-nm DNA virus that belongs to the *Hepadnaviridae* family. Hepatitis B virus (HBV) is primarily hepatotropic, and the liver damage is produced by the cellular immune response to viral proteins in infected hepatocytes. Infection with HBV causes a broad spectrum of liver disease, including subclinical infection; acute, clinically overt self-limited hepatitis; and fulminant hepatitis. The clinical manifestations of acute hepatitis B are indistinguishable from other causes of viral hepatitis; a definitive diagnosis requires serological testing. The average incubation period is 90 days (range, 60–150 days) from exposure to onset of jaundice and 60 days (range, 40–90 days) from exposure to onset of abnormal alanine aminotransferase (ALT) levels. Persons infected with HBV can also develop persistent infection, which can lead to chronic liver disease and death from cirrhosis or hepatocellular carcinoma (HCC). The age at acquisition of HBV infection is the main determining factor in the clinical expression of acute disease and the development of chronic infection (Fig. 13.1). Fewer than 10% of children younger than 5 years who become infected have initial clinical signs or symptoms of disease (i.e., acute hepatitis B), compared with 30–50% of older children and adults. The risk for developing chronic HBV infection varies inversely with age: approximately 90% of infants infected during the first year of life develop chronic infection, compared with 30% of children infected between the ages 1 and 4 years and less than 5% of persons infected as adults.

Persons who have persistence of HBsAg in serum for at least 6 months are classified as having chronic infection. HBV replication persists throughout the course of chronic HBV infection, and the natural history of chronic HBV infection is determined by the interaction between virus replication and host immune response. Persons with chronic HBV infection are at a high risk for developing HCC.

13.2 Burden of Hepatitis B

Hepatitis B virus infection is a highly prevalent infection around the globe, the frequency and burden of which vary by region and sub-

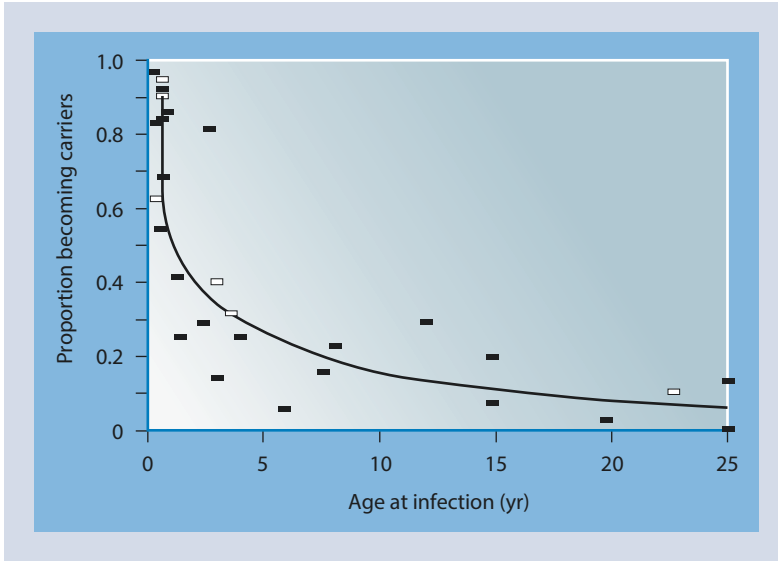


Fig. 13.1 Studies evaluating the risk for chronic hepatitis B virus infection by age at infection. *Filled squares* represent data from developing countries; *open squares* represent data from developed countries. (From Edmunds et al. 1993, with permission)

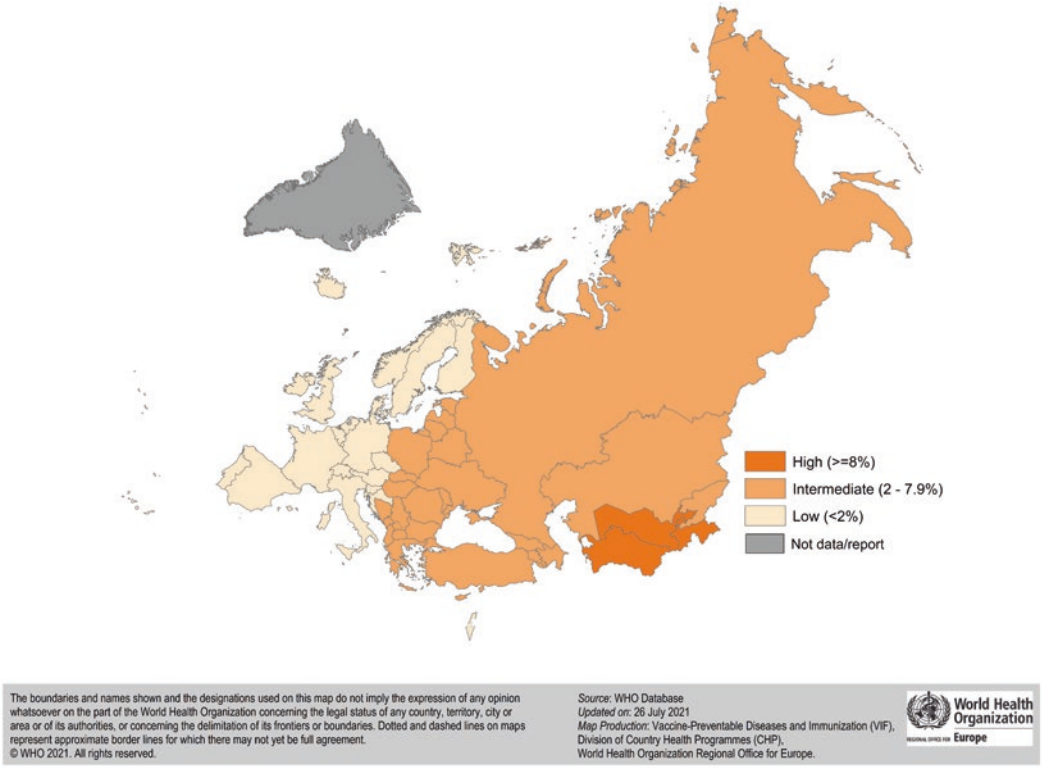


Fig. 13.2 Endemicity of hepatitis B in Europe (WHO EURO Region). (Estimated prevalence of carriage of hepatitis B surface antigen, WHO European Region)

population. Approximately 30% of the world's population (i.e., about 2 billion persons) have serological evidence for HBV infection, and of these, more than 257 million persons are living with chronic infection.

Hepatitis B virus causes significant morbidity and mortality worldwide. In 2015, approximately 887,000 HBV-infected persons died from causes related to acute infection (87,000 deaths), cirrhosis (463,000 deaths), and HBV-associated liver cancer (337,000 deaths). Of all cases of primary liver cancer, 70–90% are caused by HCC, of which HBV is a major cause. The lifetime risk for HCC in a chronically infected person is approximately 10–25%, which is 15–20 times greater than that for persons without HBV infection. As of 2016, 27 million people (10.5% of all people estimated to be living with hepatitis B) were aware of their infection. 16.7% of these diagnosed were on treatment.

In 2019 an estimated 14 million people in the WHO European Region are chronically infected with hepatitis B, leading to approximately 43,000 deaths per year from hepatitis B-related liver cancer and cirrhosis. The epidemiology of hepatitis B in the Region is diverse, with a prevalence of hepatitis B surface antigen ranging from extremely low, less than 0.1% in western, northern, and central Europe to as high as 6–8% in some countries of eastern Europe and Central Asia (Fig. 13.2).

13.3 Epidemiology

Hepatitis B virus is transmitted by percutaneous (i.e., puncture through the skin) or mucosal (i.e., direct contact with mucous membranes) exposure to infectious blood or body fluids. All hepatitis B "s" antigen (HBsAg)-positive persons are potentially

infectious, but those who are also hepatitis B "e" viral protein (HBeAg)-positive are *more* infectious because their blood contains high concentrations of HBV (typically 10^7–10^9 virions/ml). Although HBsAg has been detected in multiple body fluids, only serum, saliva, semen, and vaginal fluid have been demonstrated to be infectious. Primary sources of HBV infection are perinatal exposure from infected mothers, nonsexual person-to-person contact, sexual contact, and percutaneous exposure to blood or infectious body fluids. HBV is not transmitted by air, food, or water. The frequency and patterns of HBV transmission vary markedly in different parts of the world. In highly endemic countries, most infections are acquired during the perinatal period and early childhood, when the risk for developing chronic infection is greatest. In areas of intermediate endemicity, the lifetime risk for HBV infection is 20–60%, and infections occur in all age groups. Most HBV infections in areas of low endemicity, such as Europe, occur in adults in relatively well-defined risk groups, but a high proportion of chronic infections may occur as a consequence of perinatal and early childhood exposures. Persons considered at risk for hepatitis B are people who frequently require blood or blood products; dialysis patients; recipients of solid organ transplantations; people in closed settings, including prisoners; persons who inject drugs; household and sexual contacts of people with chronic HBV infection; people with multiple sexual partners; people living with HIV; healthcare workers; and others who may be exposed to blood and blood products through their work.

13.4 Prevention of Hepatitis B

13.4.1 Passive Immunization

A major use of hepatitis B immune globulin (HBIG; a specific immune globulin containing high concentrations of anti-HBs) is as an adjunct to hepatitis B vaccine in preventing perinatal HBV transmission. Untreated, 70–90% of infants born to HBeAg-positive mothers become infected at birth and develop chronic HBV infection. Immunoprophylaxis with both HBIG and hepatitis B vaccine confers an efficacy of preventing perinatal HBV transmission from 85% to 95% and provides long-term protection. The standard dose of HBIG is 0.5 ml for postexposure prophylaxis of infants born to HBsAg-positive mothers and 0.06 ml/kg for all other indications. HBIG should be administered intramuscularly and may be administered simultaneously with hepatitis B vaccine, but at a different injection site. HBIG is also recommended for postexposure prophylaxis (often in combination with hepatitis B vaccine) in specific settings.

13.4.2 Hepatitis B Vaccines

The first available vaccines were produced by harvesting HBsAg (the 22-nm particle) from the plasma of persons with chronic HBV infection, the so-called plasma-derived vaccines. Nowadays, these vaccines are no longer on the market. The development of recombinant DNA technology to express HBsAg in other organisms offered the potential to produce unlimited supplies of vaccine, and recombinant DNA vaccines have now completely replaced the plasma-derived vaccines. Hepatitis B vaccines are formulated to contain 2.5–40 μg of HBsAg protein and an aluminum phosphate or aluminum hydroxide adjuvant: 0.25 mg in pediatric dose vaccines and 0.5 mg in adult dose vaccines.

13.4.3 Combination Vaccines

Several vaccine manufacturers have produced combination vaccines containing a hepatitis B vaccine component. These combination vaccines include diphtheria and tetanus toxoids and whole-cell pertussis (DTwP)–hepatitis B vaccine; DTwP–*Haemophilus influenzae* type b conjugate (Hib)–hepatitis B vaccine; diphtheria and tetanus toxoids and acellular pertussis (DTaP)–hepatitis B vaccine; DTaP–Hib-inactivated poliovirus vaccine (IPV)–hepatitis B vaccine; DTaP-IPV–hepatitis B vaccine; Hib–hepatitis B vaccine; and hepatitis A–hep-

atitis B vaccine. For each of these combination vaccines, the manufacturer has shown that the components remain sufficiently immunogenic to elicit protective levels of anti-HBs (see ▶ Chap. 20).

13.4.4 Dosage and Route of Administration

The quantity of HBsAg protein per dose that induces a protective immune response in infants and children varies by manufacturer (range 2.5–10 μg) and by composition of the envelope protein(s) and is partially related to the vaccine production processes. In general, the vaccine dosage for infants and adolescents is 50% lower than that required for adults. There is no international standard of vaccine potency expressed in micrograms of HBsAg protein.

13.4.5 Vaccine Immunogenicity and Schedules

Historically, the standard three-dose hepatitis B vaccine series has consisted of two priming doses administered 1 month apart and a third dose administered 6 months after the first dose. Multiple schedules have been used successfully: at birth and at 1 and 6 months of age; at 2, 4, and 6 months; at 3, 5, and 11 months; at 8, 12, 16 weeks, and 12 or 15 months; and at 6, 10, and 14 weeks (in the World Health Organization's [WHO's] Expanded Program on Immunization [EPI] schedule).

13.4.6 Infants and Children

A variety of hepatitis B vaccine schedules have been shown to induce levels of seroprotection of greater than 95% in infants (see ▶ Sect. 4.5). Programmatically, there is an advantage to administering the three doses of hepatitis B vaccine at the same time as the three doses of other childhood vaccines (e.g., DTP, Hib, IPV), and these schedules accommodate the use of DTP-, IPV- and Hib-containing combination vaccines. To prevent perinatal HBV transmission in settings where combination vaccines are used, a four-dose hepatitis B vaccination schedule is needed, with the first dose administered at birth. Use of four-dose hepatitis B vaccine schedules, including schedules with a birth dose, has not increased vaccine reactogenicity. Certain premature infants with low birthweights (i.e., <2000 g) may have decreased seroconversion rates after administration of hepatitis B vaccine at birth. However, by the age of 1 month, all premature infants, regardless of initial birthweight or gestational age, have a response to vaccination that is comparable to that of full-term infants.

13.4.7 Adolescents

Hepatitis B vaccine schedules that have been demonstrated to induce seroprotection rates of greater than 95% in adolescents include doses administered at 0, 1, and 6 months; 0, 2, and 4 months; and 0, 12, and 24 months. In addition, for adolescents aged 11–15 years, the adult dose of hepatitis B vaccine can be used for administration at 0 and at 4–6 months. This two-dose schedule produces anti-HBs concentrations equivalent to those obtained with the pediatric dose administered on a three-dose schedule.

13.4.8 Adults

Hepatitis B vaccine induces a protective antibody response in approximately 30–55% of healthy adults aged less than 40 years after the first dose, in 75% after the second dose, and in more than 90% after the third dose. In adults older than 40 years, response rates decline with age, and by age 60 years, protective levels of antibody develop in only 75% of vaccinated persons.

13.4.9 Correlates of Protection

An anti-HBs concentration of 10 mIU/ml or more measured 1–3 months after administration of the last dose of the primary vaccina-

tion series is considered a reliable marker of protection against infection. In vaccine efficacy studies, immunocompetent persons who developed anti-HBs concentrations of 10 mIU/ml or higher after vaccination had virtually complete protection against both acute disease and chronic infection for decades, even if subsequently, over time, anti-HBs concentrations declined to less than 10 mIU/ml. Indeed, the protective efficacy of hepatitis B vaccination is related to the induction of anti-HB antibodies, but it also involves the induction of memory B and T cells. Routine postvaccination testing for immunity is not necessary, but it is recommended for high-risk persons whose subsequent clinical management depends on knowledge of their immune status. Persons at increased risk for hepatitis B found to have anti-HBs concentrations of less than 10 mIU/ml after the primary vaccine series should be revaccinated. Administration of three doses on an appropriate schedule, followed by anti-HBs testing 1–2 months after the third dose, is usually more practical than serological testing after one or more doses of vaccine.

13.4.10 Duration of Protection and Need for Booster Doses

After primary immunization with hepatitis B vaccine, anti-HBs concentrations decline rapidly within the first year and more slowly thereafter. Among children who respond to a primary three-dose vaccination series with anti-HB concentrations of 10 mIU/ml or greater, 15–50% have low or undetectable concentrations of anti-HBs 5–15 years after vaccination. Protection has been shown to outlast the presence of vaccine-induced antibodies, conferring effective long-term protection against acute disease and development of HBsAg carriage for a minimum of 25–30 years. Based on currently available scientific evidence, the WHO, in addition to advisory groups in the USA and Europe, does not recommend routine booster doses of hepatitis B vaccine or periodic serological testing to monitor anti-HBs concentrations for immunocompetent persons who have responded to vaccination or in universal immunization programs.

13.4.11 Vaccine-Associated Adverse Events

Adverse events after immunization against hepatitis B are infrequent and generally mild. With the exception of localized pain, placebo-controlled studies have revealed that reported events (e.g., myalgia and transient fever) occur not more frequently among vaccinees than among persons receiving placebo (<10% among children, 30% among adults). Data from numerous long-term studies fail to causally link serious adverse events to hepatitis B vaccination. Reports of severe anaphylactic reactions are very rare, and data do not indicate a causal association between hepatitis B vaccine and Guillain–Barré syndrome or demyelinating disorders, including multiple sclerosis.

Hepatitis B vaccine is contraindicated only for persons with a history of allergic reactions to yeast or any of the vaccine's components. Neither pregnancy nor lactation is a contraindication for use of this vaccine. Both premature infants and HIV-positive persons can receive this vaccine.

13.5 Recommendations for Hepatitis B Vaccination

13.5.1 Vaccination of Infants at Birth

Because perinatal and early postnatal transmission are primary causes of chronic infections globally, the first dose of hepatitis B vaccine should be given as soon as possible (<24 h) after birth, regardless of whether a country has low, intermediate, or high HBV endemicity. Some countries augment universal vaccination of newborns with maternal screening for HBsAg and the administration of HBIG and a dose of hepatitis B vaccine to infants born to HBsAg-positive mothers.

Among infants born to HBsAg-positive mothers, a birth dose of hepatitis B vaccine reduces the risk for perinatal HBV transmission by 72% and by >90% when combined with HBIG. The timely delivery of a birth dose of hepatitis B vaccine is now a performance measure for the global strategy on viral hepatitis as discussed in ► Sect. 13.5.4.

13.5.2 Full Immunization of Infants by Routine Immunization Programs

To complete the primary hepatitis B vaccine series, the birth dose should be followed by two or three additional doses of vaccine administered at least 4 weeks apart. To help ensure completion of the vaccine series, doses should be given concurrently with DTP or other routine infant vaccinations. For older children and adults, the primary series of three doses with appropriate intervals applies.

13.5.3 Public Health Considerations and the Impact of Worldwide Hepatitis B Vaccination Programs

Routine infant immunization has become a long-standing practice in more than 95% of countries, providing evidence for the effectiveness of hepatitis B immunization in significantly reducing or eliminating HBV transmission. In general, studies conducted in areas of high HBV endemicity have demonstrated declines in the prevalence of chronic HBV among children to less than 2% after routine infant immunization. Countries that adopted and implemented universal hepatitis B immunization early include Taiwan (1984), Bulgaria (1989), Malaysia (1990), the Gambia (1990), Italy, Spain, the USA (1991), and Israel (1992).

Taiwan is perhaps the best example of an area with previously high endemicity showing a substantial decrease in the burden of hepatitis B and HBV-related diseases after the 1984 mass vaccination of newborns. The HBsAg prevalence in individuals less than 20 years of age decreased from 9.8% in 1984 to 1.3% in 1994 and to 0.6% in 2004. The annual average incidence of HCC among children aged 6–14 years decreased from 0.7 per 100,000 in 1981 through 1986 to 0.36 per 100,000 in 1990 through 1994. In 2004, the HCC incidence for age groups of 6–9, 10–14, and 15–19 years decreased to 0.15, 0.19, and 0.16 per 100,000 person-years, respectively, clearly indicating the hepatitis B vaccine to be the first vaccine against a major human cancer.

Surveillance data from Italy, where universal vaccination started in 1991 in infants and in adolescents, have shown a clear overall decline in the incidence of acute hepatitis B, from 5/100,000 in 1990 to 0.9/100,000 in 2010. This decline was even more striking in individuals aged 15–24 years, in whom the morbidity rate per 100,000 inhabitants fell from 17 in 1990 to less than 0.5 in 2010. Moreover, a generation of children and young adults (at present, 32 age cohorts in 2011) is emerging with virtually no markers of HBV infection.

Through nationally representative serologic surveys in 1992, 2006, and 2014, also the impact of the national hepatitis B vaccination in China has been demonstrated. In persons 1–29 years, the HBV surface antigen prevalence was declined 52% by 2014. The additional efforts towards interrupting perinatal transmission by providing timely birth doses are reflected in a 97% decline of HBS surface antigen in the children <5 years of age.

13.5.4 Introduction of Hepatitis B Vaccination Programs

Despite the availability of hepatitis B vaccine since the early 1980s, barriers at that time impeded efforts to immunize infants and children against hepatitis B, for example, high vaccine costs, ill-founded concerns about using a plasma-derived vaccine during the first years of the AIDS epidemic, and the lack of global vaccine policies. By 1991, only 20 countries had implemented routine infant immunization against hepatitis B. In the following decades, hepatitis B vaccination cover-

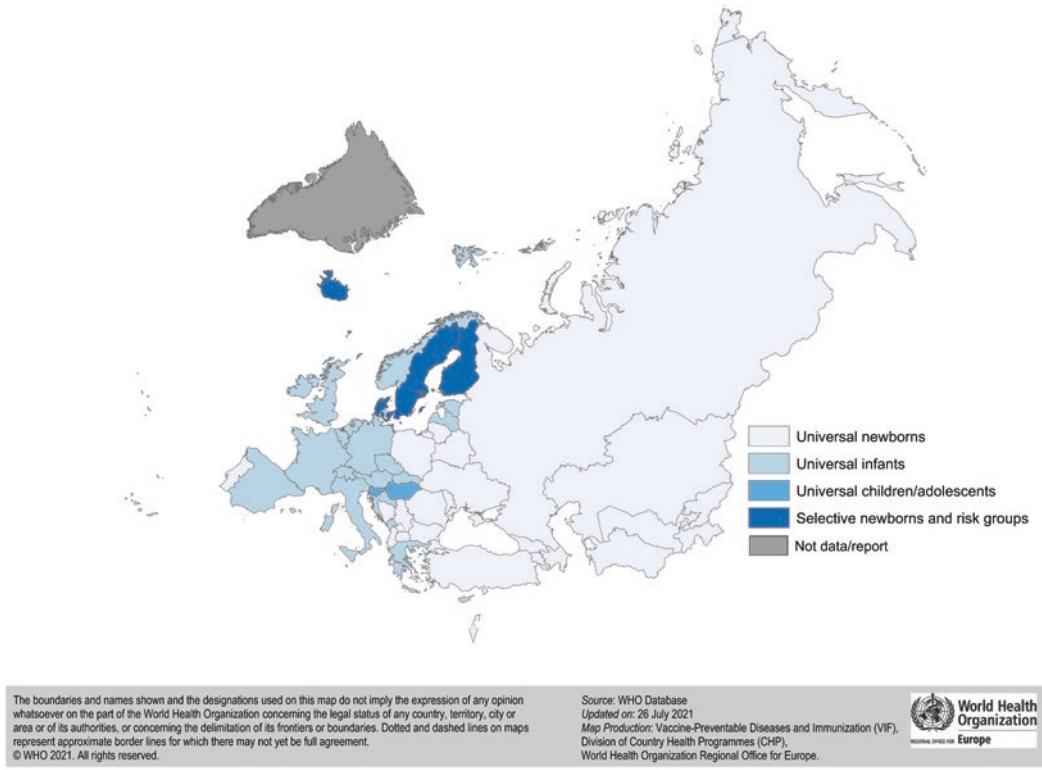


Fig. 13.3 Universal hepatitis B immunization programs in the WHO European Region, Source: WHO/UNICEF Joint Reporting Form

13

age grew rapidly, and by 2010, hepatitis B vaccination coverage among infants had reached an estimated 75% worldwide. By the end of 2019, a total of 189 countries have integrated hepatitis B vaccine into their national childhood immunization systems. Global coverage with three doses of hepatitis B vaccines is estimated at 85%.

In the WHO European Region by December 2017, a total of 50 of the 53 European countries (94%) had implemented a universal hepatitis B vaccination program (Fig. 13.3). 23 (43%) countries offered hepatitis B birth dose to all newborns, and 30 (57%) countries provided hepatitis B birth dose selectively to children born to HBsAg-positive mothers. The most recent countries to follow the recommendation were Ireland (in 2008), the Netherlands (in 2011), the UK (in 2017), and Norway (in 2017). Sweden has since 2016 regional implementation of universal hepatitis B vaccination. Still, three countries (Denmark, Finland, and Iceland) adopt vaccination targeting risk groups only, instead of adding a universal vaccination program. However, changing demography, increasing immigration, and the current vaccine costs make the cost–benefit ratios in these remaining low endemicity countries strongly in favor of universal HBV vaccination.

In May 2016, the World Health Assembly adopted the first "Global health sector strategy on viral hepatitis, 2016–2020." The strategy highlights the critical role of universal health coverage and sets targets that align with those of the Sustainable Development Goals. The strategy has a vision to eliminate viral hepatitis as a public health problem. This is encapsulated in the global targets to reduce

new viral hepatitis infections by 90% and reduce deaths due to viral hepatitis by 65% by 2030. The WHO Regional office for Europe has set hepatitis B control targets to be achieved by 2020, including 1) 90% or more coverage with three doses of hepatitis B vaccine, 2) 90% or more coverage with interventions to prevent mother-to-child transmission of HBV, and 3) 0.5% or lower than 0.5% prevalence of HBV surface antigen in age groups vaccinated with hepatitis B vaccine.

13.6 Future Vaccines

Existing hepatitis B vaccines are highly effective, and there is no evidence that new vaccines will be needed to eliminate HBV transmission with recommended immunization strategies. But – at individual level – new vaccine formulations are being developed to meet the challenges of non-response or low response to existing hepatitis B vaccines, e.g., third-generation hepatitis B recombinant vaccines containing HBsAg and pre-S1 and pre-S2 antigens or adjuvanted hepatitis B recombinant vaccines (e.g., HBsAg-1018 ISS). These vaccines are showing improved immune response in immunocompromised populations and can offer the possibility of simplified or reduced schedules, which might be very promising for the future, e.g., a 0, 1-month schedule instead of the traditional 0, 1, 6-month schedule.

Further Reading

Banatvala JE, Van Damme P. Hepatitis B vaccine: do we need boosters? J Viral Hepat. 2003;10:1–6.

Beasley RP. Hepatitis B virus: the major etiology of hepatocellular carcinoma. Cancer. 1988;61:1942–56.

Beasley RP, Hwang LY, Lin CC, et al. Hepatocellular carcinoma and hepatitis B virus: a prospective study of 22 707 men in Taiwan. Lancet. 1981;2:1129–33.

Blumberg BS, Alter HJ, Visnich S. A "new" antigen in leukemia sera. JAMA. 1965;191:541–6.

Dane DS, Cameron CH, Briggs M. Virus-like particles in serum of patients with Australia-antigen-associated hepatitis. Lancet. 1970;1:695–8.

Edmunds WJ, Medley GF, Nokes DJ, et al. The influence of age on the development of the hepatitis B carrier state. Proc Biol Sci. 1993;253:197–201.

European Centre for Disease Prevention and Control. Monitoring the responses to hepatitis B and C epidemics in the EU/EEA Member states. 2019

European Consensus Group on Hepatitis B Immunity. Are booster immunisations needed for lifelong hepatitis B immunity? Lancet. 2000;355:561–5.

European Vaccination Action Plan., available at: http://www.euro.who.int/en/health-topics/disease-prevention/vaccines-and-immunization/publications/2014/european-vaccine-action-plan-20152020. Accessed 4 Sept 2015.

Fuqiang Cui, Lipin Shen, Li Li, Huaqing Wang, et al. Prevention of Chronic Hepatitis B after 3 Decades of Escalating Vaccination Policy, China. Emerg Infect Dis 2017; 23(5): 765–772.

Goldstein ST, Zhou F, Hadler SC, et al. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. Int J Epidemiol. 2005;34:1329–39.

Hilleman MR, Buynak EB, Roehm RR, et al. Purified and inactivated human hepatitis B vaccine: progress report. Am J Med Sci. 1975;270:401–4.

Hurie MB, Mast EE, Davis JP. Horizontal transmission of hepatitis B virus infection to United States-born children of Hmong refugees. Pediatrics. 1992;89:269–73.

Institute of Medicine. Immunization safety review: hepatitis B vaccine and demyelinating neurological disorders. www.iom.edu/Reports/2002/Immunization-Safety-Review-Hepatitis-B-Vaccine-and-Demyelinating-Neurological-Disorders.aspx. May 2002.

Jilg W, Schmidt M, Deinhardt F. Vaccination against hepatitis B: comparison of three different vaccination schedules. J Infect Dis. 1989;160:766–9.

Langer-Gould A, Qian L, Tartof S, et al. Vaccines and the risk of multiple sclerosis and other central nervous system demyelinating diseases. JAMA Neurol 2014. https://doi.org/10.1001/jamaneurol.2014.2633.

Lernout T, Hendrickx G, Vorsters A, et al. A cohesive European policy for hepatitis B vaccination, are we there yet? Clin Microbiol Infect. 2014;20(Suppl 5):19–24.

Leuridan E, Van Damme P. Hepatitis B and the need for a booster dose. Clin Infect Dis. 2011;53:68–75.

Romano L, Paladini S, Van Damme P, et al. The worldwide impact of vaccination on the control and protection of viral hepatitis B. Dig Liver Dis. 2011;43(Suppl 1):S2–7.

Schweitzer A et al. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet. 2015;386:1546–1555.

Shouval D, Roggendorf H, Roggendorf M. Enhanced immune response to hepatitis B vaccination through immunization with a Pre-S1/Pre-S2/S vaccine. Medical microbiology and immunology 2015; 204(1):57.

Simons BC et al. A longitudinal hepatitis B vaccine cohort demonstrates long-lasting hepatitis B virus

(HBV) cellular immunity despite loss of antibody against HBV surface antigen. J Infect Dis. 2016;214:273–280.

Stevens CE, Taylor PE, Tong MJ, et al. Yeast-recombinant hepatitis B vaccine: efficacy with hepatitis B immune globulin in prevention of perinatal hepatitis B virus transmission. JAMA. 1987;257:2612–6.

Trépo C, Ghan HL, Lok A. Hepatitis B virus infection. Lancet. 2014;384:2953–63.

Van Damme P, Leuridan E, Hendrickx G, Vorsters A, Theeten H, Leino T, Salminen M, Kuusi M. Should Europe have a universal hepatitis B vaccination programme? BMJ. 2013;347:f4057. doi: https://doi.org/10.1136/bmj.f4057.

Van Damme P et al. Hepatitis B Vaccines, In Vaccines 7th. Plotkin SA, Orenstein WA, Offit PA editors, Elsevier Sanders, 2017.

World Health Organization. Hepatitis B vaccines. Wkly Epidemiol Rec. 2017;92:369.

World Health Organization. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Accountability for the global health sector strategies 2016-2021: actions for impact; Geneva, Switzerland: World Health Organization; 2021; Available at: https://www.who.int/publications/i/item/9789240027077.

Influenza Vaccines

Timo Vesikari and Susanna Esposito

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_14

14.1 Influenza Viruses

Influenza is caused by influenza viruses that belong to the *Orthomyxoviridae* family and have a segmented RNA genome. Influenza virus types A and B cause more than 99.9% of all the influenza cases that occur every winter season in countries with a temperate climate; influenza type C is not a significant pathogen. The incidence varies from year to year, as group A viruses may change the prevalent subtype (e.g., from H1N1 to H3N2 or vice versa), or because of antigenic "drift" within the subtype. Point mutations on genes encoding the two surface proteins of influenza viruses, hemagglutinin (HA) and neuraminidase (NA), are called antigenic drift and allow the viruses to evade immune defenses developed by individuals as a result of previous infections or vaccination. Variability due to antigenic drift is significantly more common among A viruses, in particular the A/H3N2 subtype. Influenza B viruses are more stable with regard to antigenic drift, but they frequently switch the prevalent lineage for the epidemic season (see below). Major mutations (antigenic shift) that occur only in influenza A viruses by reassortment of the RNA genome can cause pandemics because previous immunity is not effective against such a completely different virus. Examples of antigenic shift are the emergence of "Asian influenza" in 1957 (H2N2), "Hong Kong flu" in 1968 (H3N2), and "swine flu" in 2009 (H1N1sw or H1N1pdm09).

14.2 Influenza in the Pediatric Age

Influenza causes medical, social, and economic problems in children younger than 5 years of age, the elderly, pregnant women, and individuals with severe chronic medical conditions independently of age. Approximately 5–15% of the world population suffer from seasonal influenza every year, with 3–5 million severe cases and more than 500,000 deaths. Medical visits, hospitalization rates, admissions to the intensive care unit, and the prescription of drugs, antipyretics, and antibiotics are increased during influenza season, with a related impact on healthcare expenditure. School absenteeism not only has an impact on children but contributes to an average loss of 3 working days for the parent, who must remain at home with the child.

Children have the highest incidence of influenza each year. Children also shed the virus in greater amounts and for a longer time than older subjects and are considered the main contributors to the transmission of infection in the community. Although influenza in children is frequently a mild respiratory infection, it has been clearly demonstrated that influenza in healthy children may be very severe and lead to death. In a study carried out in the USA on the influenza seasons from October 2004 to September 2012, during which 830 pediatric influenza-associated deaths were reported, it was found that 43% of children who died had no high-risk medical conditions. Moreover, contrary to what was generally thought, influenza was found potentially severe not only in children younger than 5 years but also in older children and adolescents. Although the highest risk of death was associated with the first years of life (including the first 6 months), a large number of deaths occurred in children aged over 5 years.

Pregnant women are at risk for severe influenza, its complications, and death. Vaccination during pregnancy is safe and well-tolerated, does not induce fetal complications, and is highly effective in reducing the risk of influenza in young infants up to the age of 6 months (Fig. 6.2).

In the USA, the recommendation is to vaccinate all children from the age of 6 months. In Europe, only Finland and the UK have influenza vaccination as part of the national immunization program. In Finland, the program is for 6- to 36-month-old children and in the UK (using intranasal vaccine) from age 2 years up. Reduction of the burden of influenza in children can be obtained only by vaccination. Two different types of influenza vaccines are presently available: inactivated influenza vaccines (IIVs), which are given via the intramuscular and intradermal routes, and live attenuated influenza vaccines (LAIVs), which are given intranasally.

14.3 Non-live Influenza Vaccines

The technology for the first influenza vaccines dates back to 1941 and used whole influenza viruses grown in embryonated eggs and inactivated by formalin. Whole viruses have been largely replaced by split-virion vaccines or subunit (HA and NA) vaccines. Most of the influenza vaccines used in the world are still based on egg-grown virus, but are split-virion or subunit types. Cell culture-grown influenza vaccines have also been licensed, but are in the minority.

Until 2013, IIVs contained three inactivated (or split or subunit) viruses: representatives of type A/H1N1 and type A/H3N2 and one of the two genetic lineages of type B virus (Yamagata or Victoria), which had been recognized since the 1990s. Such a combination is called trivalent influenza vaccine (TIV). Specific strains to be included in the vaccine formulation are chosen every year by the WHO considering the epidemiology of virus circulation in the previous year. Inaccurate prediction of the predominant influenza B lineage left many vaccinated individuals with suboptimal protection against influenza B disease caused by the influenza B lineage not being included in the TIV. In Europe, a B mismatch between vaccine and circulating strains occurred in five out of ten seasons between 2001 and 2011. This led to a modification of the conventional composition of the influenza vaccine with the inclusion of both B lineages for a quadrivalent (or tetravalent) influenza vaccine (QIV). The quantity of HA in the vaccine is usually 15 μg per antigen. Thus, TIV contains a total of 45 μg and QIV 60 μg of HA.

Cell culture-produced IIVs are not more efficacious than egg-based vaccines, but cell culture is seen as a competitive production platform for the future. Moreover, cell culture IIVs allow the problem of egg allergy to be overcome, although the risk of severe reactions following administration of traditionally prepared IIVs to patients with an egg allergy is very low. A recent study found that the rate of anaphylaxis after all influenza vaccines, including both IIVs and LAIVs, was only 1.31 per 1 million vaccine doses given. Consequently, it was stated that influenza vaccine may be administered to patients with previous egg-associated hives without any precaution. Persons who report symptoms other than hives, such as angioedema, respiratory distress, lightheadedness, or recurrent emesis, or who required epinephrine or another emergency medical intervention may still receive influenza vaccine under close control.

Conventional TIV (or QIV) is effective, but has limitations. It has been calculated that on average prevention of influenza occurs in about 60% of vaccinated healthy adults when the circulating viruses match those in the vaccine and in approximately 40% in case of virus mismatch. Protection in older children is similar and lower in young children. Naïve children 6–36 months of age have a moderately good response to the influenza A components delivered in two half doses of TIV, but the response to B viruses is lower. All responses are poor in immunocompromised subjects or subjects with a severe chronic underlying disease with some degree of immune system deficiency. Further limitation of IIVs is the inability to evoke high antibody titers against heterovariant viruses with resulting low protection in the case of mismatch between circulating strains and strains included in the vaccines.

Usually, a half dose (7.5 μg HA) is given to infants and children aged 6–36 months, and the full dose (15 μg of each HA) is used for older children. The recommendation is to give two injections to vaccine-naïve children and a single dose annually thereafter.

A higher dose (full adult dose) of HA of each virus included in the vaccine yields a better response and greater protection in the age group 6–36 months (Table 14.1), but is not approved by the regulatory authorities. Regardless, Finland is recommending the full adult dose for its program in 6- to 36-month-old children. However, even with a higher dose, the protection against B-strains remains low.

All influenza vaccine recommendations for children start at 6 months of age. For the protection of infants aged <6 months, the

only available option is maternal immunization in pregnancy (see Fig. 6.2).

Recombinant influenza vaccines are making progress but are not yet available for children. A recombinant HA vaccine produced in baculovirus-insect cell system is licensed in the USA for persons 18 years of age and older. This vaccine, Flublok 4 (Sanofi), contains 45 μg of each of four HAs and no adjuvant. It has shown about 30% greater efficacy than standard IIV in older adults. Pediatric studies are under way.

A VLP vaccine produced in plants (*Nicotiana benthamiana*) is made by Medicago. The vaccine has shown good efficacy in adults but has not been studied in children as yet.

Table 14.1 Adult dose trivalent influenza vaccine (TIV) for young children in the Finnish National Immunization Program

Full dose TIV effectiveness by the strain		
	Influenza A	**Influenza B**
All children	84% (40–96)	45% (−34–78)
≤2 years of age	79% (21–95)	28% (−212–84)

From Heinonen et al. (2011)
Full-dose TIV for children aged 6–36 months (off-label) is efficacious against well-matched A-strains, but not B-strains

14.4 Adjuvanted IIVs

Oil-in-water emulsion adjuvants increase the immunogenicity of IIVs. The best-known adjuvant is MF59, which contains squalene. MF59 has been extensively studied and is currently licensed for use in the elderly in many EU countries. The MF59-adjuvanted trivalent seasonal influenza vaccine (aTIV) has been evaluated in young children for immunogenicity, safety, and efficacy. MF59-adjuvanted vaccine was safe and well-tolerated with only a small, clinically marginal increase in local adverse events. aTIV was highly efficacious in all children under 6 years of age and significantly more efficacious than a TIV comparator (Fig. 14.1). In the specific age group 6–24 months, aTIV was efficacious, whereas TIV was not. Immune responses against B-strains were high after two doses of aTIV. MF59 adjuvant also increases the heterovariant immune responses to A-strains not included in the vaccine.

Despite the promising results, aTIV was not licensed in the EU for children. It is licensed in Canada and recommended for age group 6–23-month-old. Studies have been continued with a quadrivalent formulation of MF59-adjuvanted vaccine (aQIV), and there is a reasonable expectation that this vaccine may be licensed for EU children in the near future.

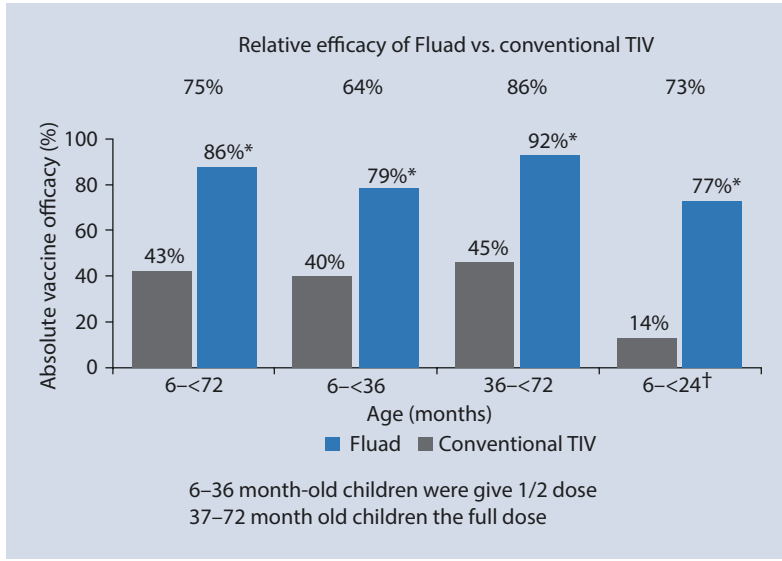


Fig. 14.1 Efficacy of MF59-adjuvanted (aTIV) vaccine in children according to age in a multicenter trial in Finland and Germany. *Statistically significant result, †Post hoc analysis. (From Vesikari et al. 2011)

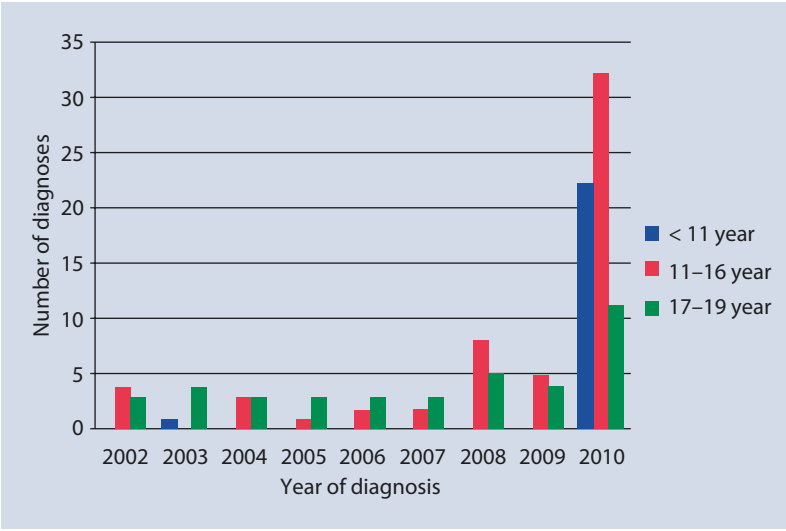


Fig. 14.2 Increase in newly diagnosed cases of narcolepsy in 4- to 19-year-old children and adolescents in Finland in 2010 after extensive vaccinations against H1N1pdm09 virus in the fall of 2009 using an AS03-adjuvanted vaccine. (Partinen et al. 2012)

Virosomes, which are reconstituted viral envelopes including membrane lipids and viral spike glycoproteins, but devoid of viral genetic material, were used for preparation of adjuvanted influenza vaccines until few years ago. Several studies showed a significant improvement in the immune response in comparison with conventional IIVs in subjects of any age. However, the virosome vaccine was withdrawn from the market, mainly because its administration in younger children was followed by high fever in a non-negligible number of subjects.

14.5 Pandemic H1N1sw Vaccine and Narcolepsy

In 2009, with the emergence of "swine flu" of the H1N1sw pandemic, vaccines against this strain were hastily produced and implemented with a minimal delay. Conventional split-virion or subunit vaccines were not sufficiently immunogenic, whereas whole-virion vaccine was reasonably immunogenic, but of limited supply. MF59-adjuvanted H1N1sw vaccine was used to some extent in Europe, but more extensively outside. In contrast, a vaccine with a "stronger" adjuvant, AS03, which contains both squalene and α-tocopherol, was introduced into several European countries. Such a vaccine was highly immunogenic but also reactogenic in children. It was used extensively and showed high effectiveness in all age groups.

In 2010, the AS03-adjuvanted H1N1sw vaccine (Pandemrix) was found to be associated with narcolepsy, which is one of the greatest vaccine disasters of modern times. Narcolepsy is a permanent and debilitating condition. First reported in Sweden and Finland, narcolepsy was seen in many other countries using the Pandemrix vaccine (but not in connection with other vaccines). The vaccine increased the risk of narcolepsy in genetically susceptible subjects, mainly in the age range of 5–19 years, to at least 13-fold the background risk (Fig. 14.2). A similar increase in narcolepsy was not seen in Canada, where another AS03-adjuvanted H1N1sw vaccine (Arepanrix) was used.

The underlying mechanism may be related to the production process of the split-virion vaccine in Europe, resulting in a high content of the influenza nucleoprotein (NP) antigen in the vaccine. NP may be polymerized, and in the presence of a strong adjuvant such as AS03, a very strong immune response in young people is induced not only against the HA and NA antigens but also NP, which in turn may result in the induction of autoimmune reaction in susceptible individuals, with cross-reactivity against hypocretin receptor 2, leading to deficiency of hypocretin and clinical narcolepsy. Recent studies have shown

molecular mimicry at T-cell level both in nucleoprotein and neuraminidase peptides of H1N1sw virus and hypocretin reseptor 2. The role of ASO3 adjuvant in the induction of narcolepsy also appears likely.

14.6 Live Attenuated Influenza Vaccine

In the past few years, LAIVs became an option for annual immunization against seasonal influenza in children. The current vaccine (the only one available in Europe) is based on cold-adapted (*ca*) temperature-sensitive (*ts*) mutants that were developed by HF Maassab in 1966. The *ca*, *ts* parent strains for influenza A and B are reassorted with the HA and NA genes of current seasonal influenza viruses to make 6:2 reassortants of influenza A and B, respectively, that contain six genes from the *ca* and *ts* parents and retain the characteristics of the parent strain. The parent strains grow well in embryonated eggs, which are used for vaccine production.

The parent strains for *ca* and *ts* influenza virus strains were developed separately for influenza A and B viruses in primary chicken kidney cells by serial passages at successive (down to 25 °C) temperatures. The parent strains are stable and retain the mutations responsible for *ca* and *ts* phenotypes upon serial passages in animals and after replication in humans. The *ca* phenotype refers to the ability to grow at 25 °C and *ts* to no growth at 39 °C for influenza A and 37 °C for influenza B. In practice, this means that LAIV viruses are able to multiply on mucous membranes of the upper airways, but not in the lungs.

Traditionally, the *ca*, *ts* parent strains were reassorted with the HA and NA genes of epidemic influenza viruses by co-infection in eggs, to create 6:2 reassortants for influenza A and B vaccines, respectively. Since 2006, a new technology, reverse genetics, has been used instead. This technology enables modification of the HA gene before production and incorporation in the vaccine and has been used to improve the yield and thermostability of the vaccine strains.

14.6.1 Efficacy

A trivalent composition of LAIV (CAIV-T, LAIV3) was tested in a number of efficacy trials before licensure in 2007. The current quadrivalent formulation LAIV4 was not tested for efficacy before licensure in 2013, but real-life effectiveness data are available from several sources and, in fact, suggest that LAIV4 has not performed so well in 2013–2016 as LAIV3 did before.

A placebo-controlled efficacy trial in 8- to 36-month-old day care children was conducted in six European countries in 2000–2001 and forms the basis for expectations of LAIV performance. The study lasted for two influenza epidemic seasons. Before the first season, all children received two doses of LAIV3 and before the second season, one dose. This is how the LAIV should be administered, but often is not. Laboratory-confirmed influenza occurred in over 10% of the subjects in the first year and about 20% in the second year, indicating the high incidence of influenza in young children and hence the need to vaccinate.

The composite vaccine efficacy in the first and second years, respectively, was 85.4% and 88.7%. The strain-specific efficacy is shown in Table 14.2. Efficacy against A-strains was at least 90% and against B-strains 70–80%, even though some of the circulating B-strains were of a different lineage.

Several other LAIV3 efficacy trials were performed against the TIV comparator, and

Table 14.2 Efficacy of live attenuated influenza vaccines (LAIV)3 in a European multicenter trial in 8–36-month-old day care children

Strain	Vaccine efficacy
A/H1N1, season 2001	91.8% (80.8, 97.1)
A/H3N2, season 2002	90.3% (82.9, 94.9)
B, season 2002 Mixed Yamagata and Victoria	81.7% (53.7, 93.9)

Modified from Vesikari et al. (2006a)

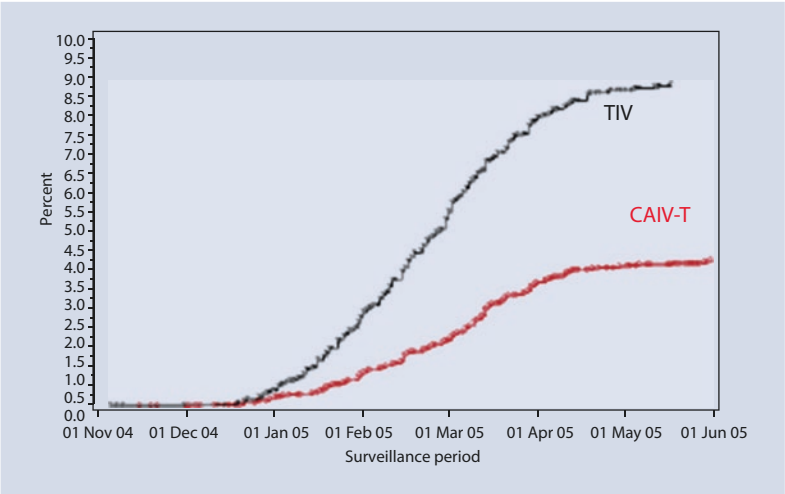


Fig. 14.3 Cumulative occurrence of culture-confirmed influenza during one influenza season in 6- to 59-month-old children vaccinated with two doses of TIV or LAIV (CAIV-T). (From Belshe et al. 2007)

each showed a greater efficacy in children. The pivotal trial carried out in 8,475 children aged 6–59 months is shown in Fig. 14.3. LAIV3 given in two doses to vaccine-naïve children (about two thirds of the study population) showed 54% greater efficacy than TIV; if it was assumed that the efficacy of TIV might have been about 50%, then the efficacy of LAIV3 amounts to around 80% against any strain.

14.6.2 Real-Life Effectiveness

Because of safety issues (see below), LAIV is licensed only for children above 2 years of age. Accordingly, LAIV has been used increasingly in the USA and Europe in children above this age. In the UK, a recommendation was issued in 2013 to give a single dose of LAIV to children aged 2–17 years; in practice, the introduction of this program has now reached ages 2–9 years. In Finland, LAIV has been given since 2014 to children as part of the national immunization program and is now given to ages 2–7 years. In most cases in the USA and exclusively in the UK and Finland, a single dose of LAIV has been given, which is not what had been studied in prelicensure trials of LAIV.

Matters were complicated by two issues:

1. In 2009, the H1N1pdm09 pandemic strain was introduced into the LAIV to replace an earlier H1N1 component. The HA of the H1N1pdm09 turned out to be thermolabile, which may have been the reason for reduced vaccine effectiveness discovered several years later.
2. A quadrivalent composition of LAIV (LAIV4) was introduced in 2013. This vaccine contained two B-strains representing Victoria and Yamagata lineages. The logic behind this was the same as for non-live influenza vaccines: to increase coverage against influenza B. However, the real-life value of the quadrivalent composition was not tested in an efficacy trial, but the US Food and Drugs Administration approved the LAIV4 vaccine based on immunogenicity only. In Europe, the European Medicines Agency, unlike for QIV, did not require an efficacy trial for LAIV4 either.

The real-life effectiveness follow-up in the USA (US Flu Vaccine Effectiveness Network) was lower than expected, compared with prelicensure efficacy. Since 2013, the LAIV4 composition did not show any efficacy against influenza A (largely H1N1) at all. This led to withdrawal of the recommendation of LAIVs by the Advisory Committee on Immunization Practices in June 2016, but recommendation was back in place for the 2018–2019 season.

In Europe, a case-control study of LAIV4 in the UK in the age group 2–7 years showed an adjusted vaccine efficacy of 57.6% (25.1–76%) against laboratory-confirmed influenza. Since then effectiveness has been between 27% and

67% depending on the season. In Finland, an overall vaccine effectiveness of 51% was found in the season 2015–2016.

Altogether, real-life effectiveness of LAIV4 has been systematically lower than what was found in the efficacy studies of CAIV3.

14.6.3 Safety

LAIVs continued to be used in 2016–2017 season in the UK and Finland immunization programs despite their relatively low efficacy. In general, it would seem prudent to follow the US recommendation not to continue the use of LAIVs until the reasons for low performance have been fully elucidated and the problems corrected.

Three safety issues are related to LAIVs:

1. Flu-like symptoms associated with the multiplication of live attenuated viruses in the upper respiratory tract. This issue is also related to the shedding and potential transmission of vaccine viruses to susceptible subjects in the environment.
2. Provocation of asthma or asthma-like wheezing in asthma-prone children.
3. Increased hospitalizations, owing to respiratory problems and other reasons in subjects under 12 months of age.

Respiratory symptoms occur in about 10% of naïve children 3–7 days after administration of LAIVs and usually last 2–3 days. The symptoms include runny and stuffy nose and mild fever. The vaccine seems to protect against itself: flu-like symptoms are rare after the second dose.

Shedding of the vaccine virus may be detected in up to 70% of susceptible children. The B-strain is dominant over A-strains. Shedding peaks between days 3 and 10, but may last up to 3 weeks. Transmission is, however, rare. Of note, if the vaccine virus is transmitted, it retains the *ca*, *ts* phenotype and does not cause significant symptoms in the recipients.

Asthma-like wheezing is the best-known side effect of LAIVs, which has limited the use of this vaccine in children aged 24 months and older. Characteristically, the wheezing period occurs 7–14 days after administration of LAIVs (Fig. 14.4).

Wheezing is mainly limited to asthma-prone children under 24 months of age; although it may occur in older children, the rate is not significantly higher than in controls. In younger children, about one half of the wheezing episodes are mild, but the other half are not and some may require hospitalization. Therefore, the current LAIVs should not be given to children younger than 24 months of age.

The increased rate of hospitalization in recipient children aged 6–11 months is largely unexplained. It is likely related to the insufficient attenuation of LAIV for the youngest infants.

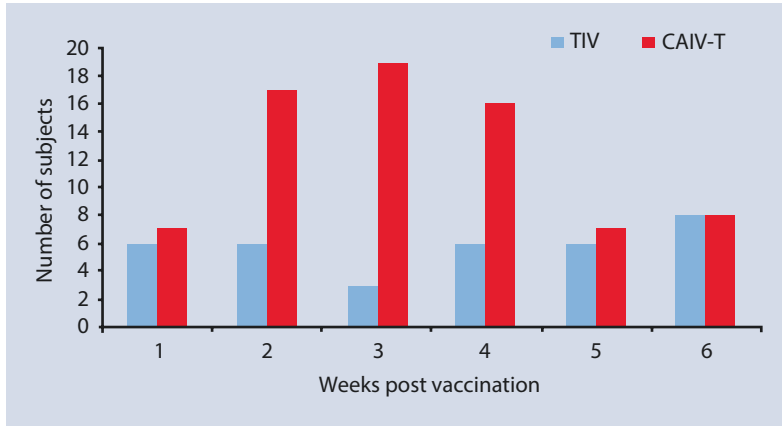


Fig. 14.4 Episodes of wheezing in children aged 6–59 months vaccinated with TIV or LAIV (CAIV-T)

14.6.4 Other LAIVs

Another LAIV, based on the cold-adapted H2N2 virus backbone, was developed in Russia ("Leningrad strain") and recently licensed to manufacturers in China and India. The intranasal vaccine has been tested and extensively used in Russia, but not outside that country. The H2N2 backbone has been used to generate 6:2 reassortants of a variety of seasonal influenza A-strains and pandemic influenza strains. The vaccine can be produced in cell culture.

Further Reading

Ambrose CS, Yi T, Falloon J. An integrated, multistudy analysis of the safety of Ann Arbor strain live attenuated influenza vaccine in children aged 2–17 years. Influenza Other Respir Viruses. 2011;5:389–97.

Belshe RB, Edwards KM, Vesikari T, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. N Engl J Med. 2007;356:685–96.

Centers for Disease Control and Prevention. Influenza (Flu). Flu vaccine and people with egg allergies. Available at: https://www.cdc.gov/flu/protect/vaccine/egg-allergies.htm. Accessed on: 12 March 2017.

Chen J, Deng YM. Influenza virus antigenic variation, host antibody production and new approach to control epidemics. Virol J. 2009;6:30.

Dunkle LM, Izikson R, Patriarca P et al. Efficacy of recombinant influenza vaccine in adults 50 years of age or older. N Engl J Med 2017;376:2427−36.

Durando P, Icardi G, Ansaldi F. MF59-adjuvanted vaccine: a safe and useful tool to enhance and broaden protection against seasonal influenza viruses in subjects at risk. Expert Opin Biol Ther. 2010;10:639–51.

Esposito S, Marchisio P, Ansaldi F, Bianchini S, Pacei M, Baggi E, et al. A randomized clinical trial assessing immunogenicity and safety of a double dose of virosomal-adjuvanted influenza vaccine administered to unprimed children aged 6–35 months. Vaccine. 2010;28:6137–44.

Heinonen S, Silvennoinen H, Lehtinen P, Vainionpää R, Ziegler T, Heikkinen T. Effectiveness of inactivated influenza vaccine in children aged 9 months to 3 years: an observational cohort study. Lancet Infect Dis. 2011;11:23–9.

Jon H, Chen Z. Production of live attenuated influenza vaccines against seasonal and potential pandemic influenza viruses. Curr Opin Virol. 2014;6:34–9.

Lin Y, Wen C, Lin Y et al. Oil-in-water emulsion adjuvants for pediatric influenza vaccines: a systematic review and meta-analysis. Nat commun 2020;11:315.

Maassab HF, DeBorde DC. Development and characterization of cold-adapted viruses for use as live virus vaccines. Vaccine. 1985;3:355–69.

Murphy BR, Coelingh K. Principles underlying the development and use of live attenuated cold-adapted influenza A and B virus vaccines. Viral Immunol. 2002;15:295–323.

Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis. 2012;12:36–44.

Partinen M, Saarenpaa-Heikkila O, Ilveskoski I, et al. Increased incidence and clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaign in Finland. PLoS One. 2012;7:e33723.

Peasah SK, Azziz-Baumgartner E, Breese J, Meltzer MI, Widdowson MA. Influenza cost and cost-effectiveness studies globally – a review. Vaccine. 2013;31:5339–48.

Principi N, Esposito S. Adjuvanted influenza vaccines. Hum Vaccin Immunother. 2012;8:59–66.

Principi N, Esposito S. Protection of children against influenza: emerging problems. Hum Vaccin Immunother. 2017;27:1–8: doi: https://doi.org/10.1080/21645515.2017.1279772.

Rudenko LG, Slepushkin AN, Monto AS, et al. Efficacy of live and inactivated influenza vaccine in school children and their unvaccinated contacts in Novgorod, Russia. J Infect Dis. 1993;168:881–997.

Sakala IG, Honda-Okubo Y, Fung J, Petrovsky N. Influenza immunization during pregnancy: benefits for mother and infant. Hum Vaccin Immunother. 2016;12:3065–71.

Sarkanen TO, Alakuijala APE, Dauvilliers YA, Partinen MM. Incidence of narcolepsy after H1N1 influenza and vaccinations: systematic review and meta-analysis. Sleep Med Rev 2018;38:177−86.

Vaarala O, Vuorela A, Partinen M, Baumann M, Freitag TL, Meri S, et al. Antigenic Differences between AS03 Adjuvanted Influenza A (H1N1) Pandemic Vaccines: Implications for Pandemrix-Associated Narcolepsy Risk. PLoS One. 2014;9(12):[114361]. https://doi.org/10.1371/journal.pone.0114361.

Vesikari T, Fleming DM, Aristegui JF, et al. Safety, efficacy, and effectiveness of cold-adapted influenza vaccine-trivalent against community-acquired, culture-confirmed influenza in young children attending day care. Pediatrics. 2006a;118:2298–312.

Vesikari T, Karvonen A, Korhonen T, et al. A randomized, double-blind study of the safety, transmissibility and phenotypic and genotypic stability of cold-adapted influenza virus vaccine. Pediatr Infect Dis J. 2006b;25:590–5.

Vesikari T, Pellegrini M, Karvonen A, Groth N, Borkowski A, O'Hagan DT, et al. Enhanced immunogenicity of seasonal influenza vaccines in young children using MF59 adjuvant. Pediatr Infect Dis J. 2009;28:563–71.

Vesikari T, Knuf M, Wutzler P, et al. Oil-in-water emulsion adjuvant with influenza vaccine in young children. N Engl J Med. 2011;365:1406–16.

Vuorela A, Freitag TL, Leskinen K, Pessa H, Härkönen T, Stracenski I, et al. Enhanced influenza A H1N1 T cell epitope recognition and cross-reactivity to protein-O-mannosyltransferase 1 in Pandemrix-associated narcolepsy type 1. Nature Communications. 2021;12(1):[2283]. https://doi.org/10.1038/s41467-021-22637-8.

WHO. Vaccines against influenza WHO position paper – November 2012. Weekly Epidemiol Rec. 2012;87:461–76.

Human Papillomavirus Vaccines

Paolo Bonanni

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_15

15.1 Burden of HPV-Related Diseases in the Pre-vaccination Era

Human papillomaviruses (HPVs) include more than 100 viral types, with tropism for mucosa or skin. Infection with HPVs may become persistent and progress to precancerous lesions and eventually to invasion, causing cancers in a variety of sites, including the uterine cervix, vulva, vagina, penis, anus, oral cavity, oropharynx, and possibly the skin in patients with epidermodysplasia verruciformis. In order to evaluate the baseline levels of HPV infections and related diseases before universal vaccination programs were implemented, it is necessary to refer to data collected in the years 2003–2012. At that time, HPV infections were estimated to account for 5.2% of all cancers in the world, being responsible for 3% of mouth, 12% of oropharynx, 40% of penis, 40% of vulva/vagina, and virtually 100% of uterine cervix cancers. In particular, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 are classified as group 1 carcinogens by the International Agency for Research on Cancer (IARC). Cervical cancer was the fourth most common cancer in women, and the seventh overall, with an estimated 528,000 new cases in 2012. Most (around 85%) of the global burden occurs in low- and middle-income countries (LMIC), where it accounts for almost 12% of all female cancers. There were an estimated 266,000 deaths from cervical cancer worldwide in 2012, comprising 7.5% of all female cancer deaths. Almost nine out of ten (87%) cervical cancer deaths occurred in the LMIC regions. Mortality varies 18-fold among the different regions of the world, with rates ranging from less than 2 per 100,000 in Western Asia, Western Europe, and Australia/New Zealand to more than 20 per 100,000 in Melanesia (20.6), Middle (22.2), and Eastern (27.6) Africa. In addition to causing malignant cancers, HPVs are also the cause of genital warts (GWs), histologically benign lesions that represent the most common sexually transmitted disease in many countries. Several million cases of GWs occur every year in the world in both females and males, with a peak incidence between 20 and 24 years of age for women and between 25 and 29 years among men. HPVs are also responsible for a very rare but extremely debilitating disease, juvenile-onset recurrent respiratory papillomatosis (JORRP), characterized by the growth of recurrent tumors in the respiratory tract, which results from a vertical transmission of HPV from mother to child. Virology studies have substantiated the link between genital condylomas and JORRP. HPV types 6 and 11, which are responsible for 80–90% of the condylomas, are responsible for nearly 100% of JORRP.

European data (2012) (▶ http://www.hpvcentre.net/statistics/reports/XEX.pdf) confirm that the disease burden due to HPV infection is impressive: more than 58,000 new cervical cancer cases are estimated to be diagnosed annually, i.e., the sixth cause of female cancer in Europe overall and the second most common female cancer in women aged 15–44 years. Looking at mortality, more than 24,000 new cervical cancer deaths occur annually in Europe, i.e., the seventh cause of female cancer death overall and the second most common cause of female cancer death in women aged 15–44 years.

Data on other HPV-related cancers are more difficult to obtain, owing to their relatively lower incidence and to a lack of standardization of registries. However, estimates performed using reliable information available for 26 countries in Europe (EU countries not including Greece, Hungary, Luxemburg, and Romania plus data from Iceland, Norway, and Switzerland) show an incidence of about 2700 vulvar cancers, 1100 vaginal cancers, 4600 anal cancers (2900 in females, 1700 in males), 15,200 head and neck cancers (2500 in females, 12,700 in males), and almost 1100 penile cancers. In the same countries, 23,200 cervical cancer cases are estimated to occur every year. Overall, this means that, of the 48,000 HPV-16- and HPV-18-related cancers occurring each year in the selected European countries, 30% are in men. Excluding cervical cancer, of the approximately 23,000 cancer cases due to HPV-16/18, most are seen in men owing to the incidence

of head and neck cancers, which are fivefold more frequent in males than females. New cases of GWs attributable to HPV types 6/11 in the same countries are estimated at between 615,000 and 675,000 each year, with an equal sex distribution.

Regarding precancerous lesions, data collected between 2003 and 2007 in the 31 countries covered by the European Medicines Agency plus Switzerland showed the following ranges in numbers attributable to HPV: Cervical Intraepithelial Neoplasia (CIN) grade 2 or higher (CIN2+) 267,350–510,609; Vulvar Intraepithelial Neoplasia grade 2/3 (VIN 2/3) 12,067–23,977; Vaginal Intraepithelial Neoplasia grade 2/3 (VaIN 2/3) 2442–4521; and Anal Intraepithelial Neoplasia grade 2/3 (AIN 2/3) 1545 in females and 1093 in males.

15.2 Epidemiology and Ways of Transmission

The association between persistent HPV infection and cervical cancer is one of the strongest known in epidemiology, meaning that cervical cancer is necessarily linked to such an infection. HPV types 16 and 18 are responsible for >70% of cervical cancers in the world, the remaining less than 30% being due to the other carcinogenic types. The fraction of noncervical cancers attributable to HPV is variable, being about 83% for anal cancer, 60% for vaginal cancer, 42% for penile cancer, 31% for vulvar cancer, and 22% for oropharyngeal cancer. HPV-16 is also the single most important type to which almost all noncervical cancers due to HPV are attributable.

HPV-6 and HPV-11 are responsible for >90% of genital warts and JORRP cases in the world.

Several co-factors linked to the possible evolution from persistent infection toward precancerous and cancerous lesions have been recognized: smoking, parity, use of oral contraceptives, HIV infection, and other sexually transmitted infections. Male circumcision has been shown to decrease the risk of cervical cancer in female partners.

Transmission of HPV occurs primarily through sexual intercourse, not necessarily implying penetration. As a matter of fact, infection has also been described following manual–genital or oral–genital contact. Condom use may reduce the risk of infection, but is not completely protective.

In addition, nonsexual routes are possible, the most important being mother-to-child vertical transmission, which is a rare but possible event. Transmission through contaminated objects (i.e., surgical gloves or biopsy forceps) has been hypothesized, but has never been definitely proven.

15.3 Human Papillomavirus Vaccines

The development of HPV prophylactic vaccines started after the demonstration of the possibility of producing virus-like particles (VLPs) through self-assembly of antigens codified by the genomic regions L1 and L2 (virus capsid proteins). This property is one of the reasons for the high immunogenicity of HPV vaccines, as recombinant L1 proteins produced in yeast or insect cells reconstitute the external shell structure of the virus.

Infection with HPV is an exclusively mucosal event (no viremia) that does not cause inflammation or cell death. Consequently, natural immunity following infection is usually weak, and reinfection with the same HPV type may occur. Vaccination is given intramuscularly, and a strong primary and secondary response (including immunological memory induction) is obtained after a complete course of immunization.

The mechanism of protection is based on neutralizing antibodies able to prevent virus entry into the target mucosal cell. It is postulated that anti-HPV antibodies produced following active immunization transudate into the cervical mucosal basal layer and into the cervical mucus, where virions are neutralized. However, no minimum protective level of antibodies (correlate of protection) has been defined, also as a consequence of the excellent protection afforded by vaccines. The lack of

such a correlate implies that the protective effect of vaccines needs to be defined clinically. As it is not possible to measure the efficacy of HPV vaccines against cervical and other cancers in clinical trials for evident ethical and temporal reasons, it was necessary to find a surrogate marker of protection afforded by vaccination. Persistent infection with HPV is a possible outcome, but viral clearance can occur spontaneously. Prevention of cervical intraepithelial neoplasia (CIN) grade 2 or higher (CIN2+) is considered the best surrogate, as spontaneous reversion to normal histology, although possible, is very rare.

The demonstration of immunogenicity, efficacy, and safety of the first prototype monovalent vaccine against HPV-16 paved the way for the development and availability of first-generation vaccines, i.e., the quadrivalent vaccine (containing HPV types 6, 11, 16, and 18) and the bivalent vaccine (containing HPV types 16 and 18). Since 2015, a nine-valent HPV vaccine (containing HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58) has been approved for use in the USA and Europe.

Table 15.1 Efficacy of the nine-valent human papilloma virus (HPV) vaccine against HPV-31/33/45/52/58 (cervical/vulvar/vaginal disease, persistent infection) – women aged 16–26 years; received all three vaccinations within year of enrolment

Per protocol efficacy population (median follow-up 40 months post dose 33)			
Endpoint	**9vHPV vaccine No. of cases/*n***	**qHPV vaccine No. of cases/*n***	**Efficacy (95% CI)**
≥CIN2/3, VIN2/3, VaIN2/3	1/6016	30/6017	96.7% (80.9, 99.8)
All CIN, VIN, VaIN2	3/6016	103/6017	97.1% (91.8, 99.2)
6-month persistent infection	35/5939	810/5953	96.0% (94.4, 97.2)

1. Joura et al. (2015)
2. Supplement for Joura et al. (2015)
3. Bautista O. V503–001 MEMO – Median Follow-up Time for Efficacy. Data on file. Dr. A Luxembourg ACIP February 2014 Meeting. ► http://www.cdc.gov/vaccines/acip/meetings/slides-2016-02.html

15.4 Bivalent HPV Vaccine

The bivalent vaccine, Cervarix (GSK), is produced in insect cells (derived from the butterfly *Trichoplusia ni*) by recombinant DNA techniques and adjuvanted with the AS04 system, which is composed of aluminum hydroxide and monophosphoryl lipid A, a lipopolysaccharide from the cell wall of *Salmonella* spp. bacteria (Table 15.1). Efficacy data were evaluated in a young adult female population after a three-dose schedule at 0, 1, and 6 months of the vaccine or placebo. Efficacy was primarily in the total vaccinated cohort, which included women who were HPV-DNA-negative and seronegative for HPV-16 and HPV-18 at study entry and who had received at least one dose of vaccine or placebo. Women who had a baseline high-grade lesion or lacking cytology data were excluded from the analysis. The efficacy of the bivalent vaccine in the prevention of CIN2+ associated with HPV-16 and/or HPV-18 was 90.4% (97.9% confidence interval [CI] 53.4–99.3%). Efficacy against the single types was 93.3% (97.9%; CI 47.0–99.9%) for HPV-16 and 83.3% (97.9% CI −78.8–99.9%) for HPV-18. When the analysis was also based on HPV-16 or HPV-18 in the lesion and in preceding cytology samples (post hoc analysis with attribution of the lesion to specific HPV types), efficacy values all became 100% (97.9% CI 74.2–100% for type 16/18; 64.5–100% for type 16; −49.5 to 100% for type 18). The bivalent HPV vaccine showed a cross-protective efficacy, especially against types 31 and 45. An overall efficacy against CIN3+ lesions (irrespective of HPV type in the lesion) of 93.2% (95% CI 78.9–98.7%) was reported at year 4 of follow-up for women involved in the PATRICIA clinical trial. However, it is not possible to define the duration of such a cross-protective effect, also because the clinical trials of HPV vaccines were not powered with the aim of measuring cross-protection. A comparative study on the

immunogenicity of the bivalent and the quadrivalent HPV vaccines showed significantly higher levels of antibodies against both HPV-16 and HPV-18 following administration of the bivalent versus the quadrivalent vaccine. The meaning of such data for long-term protection is as yet unknown.

Following a specifically designed clinical trial to compare the immunogenicity of two doses of bivalent vaccine in girls 9–14 years of age vs three doses given to young women aged 15–25 years, which demonstrated that GMTs after two doses in girls were not inferior to three doses in women, a change occurred in the recommended schedule for young girls, which since 2013/2014 foresees the administration of two doses at 6 months apart for subjects aged <15 years.

15.5 Quadrivalent HPV Vaccine

The quadrivalent vaccine (Gardasil, Merck) is produced in yeast cells by recombinant DNA techniques and adjuvanted with amorphous aluminum salts (Table 15.1). The phase 3 clinical trial was performed in 13 different countries (FUTURE II Study) and involved about 12,000 women, randomly assigned to receive HPV vaccine or placebo according to a 3-dose schedule (0, 2, and 6 months). The composite efficacy result (CIN2, CIN3, adenocarcinoma in situ) after an average 3-year follow-up was 98% (95% CI 86–100%) in the per-protocol susceptible population and 44% (95% CI 26–58%) in the intention-to-treat population, where women already infected were also represented.

Immunological memory against the quadrivalent L1-encoded HPV antigens was demonstrated by a challenge dose administered 5 years after the first dose in fully vaccinated women. A booster response was elicited even if the woman had lost detectable antibodies to some antigen. Interestingly, in the same study, it was possible to highlight that no case of breakthrough infection occurred in women of the vaccine group who became seronegative in the 5-year time interval, whereas ten cases of infection occurred in women belonging to the placebo group. It is not clear whether this means that vaccinated women retained a protective but undetectable level of antibodies to the L1 antigen, or if they were protected through an anamnestic response at the mucosal level. Women belonging to the placebo group were immunized at year 5, and this intervention prevented the possibility of having long-term efficacy data through the comparison of vaccinated vs unvaccinated women. However, data from originally vaccinated women followed through cancer registries in Nordic countries demonstrated no breakthrough infection after 12 years of follow-up, with a trend toward continued protection through 14 years post-vaccination. The quadrivalent vaccine showed a good degree of cross-protection in clinical trials, especially against HPV-31 and HPV-33, the duration of which needs to be further investigated. An independent study comparing the antibody response obtained after two doses administered 6 months apart in girls aged 9–13 years versus young women aged 16–26 years receiving three doses at 0, 2, and 6 months showed non-inferiority of the two-dose schedule, and the two-dose schedule was approved for the quadrivalent vaccine given at age 9–13 years.

15.6 Nonavalent HPV Vaccine

The nine-valent HPV vaccine was developed based on the heritage of the quadrivalent vaccine, with which it shares the same production process and the same adjuvant. It includes the additional HPV types 31, 33, 45, 52, and 58. The foreseen direct impact of the new vaccine is an increase in prevented overall HPV-related cancers from 75% to 89%. About 90% of cervical cancer cases are directly preventable using the nine-valent vaccine (vs 72% with the quadrivalent vaccine), whereas the increase in prevented cases would be more limited for anal cancer (from 87% to 90%).

In a double-blind, randomized, multicenter study, over 14,000 women were randomly assigned to receive three doses of either the nonavalent or the quadrivalent HPV vaccine (comparator) at months 0, 2,

and 6. The nonavalent vaccine turned out to have overlapping (and non-inferior) seroconversion rates and geometric mean titers (GMTs) 1 month after the third dose (month 7). The efficacy of the nonavalent vaccine against precancerous lesions and persistent infection due to HPV types 31, 33, 45, 52, and 58 was directly measured in the trial, as the quadrivalent vaccine lacks VLPs of such HPV types. The overall efficacy data against different endpoints for the five types are reported in Table 15.1 and was invariably >90%, mostly >95%. Table 15.2 reports the 6-month efficacy against persistent infection for the single additional types of the nine-valent vaccine, which ranged from 94.8% to 99.1%.

Table 15.2 Efficacy of the nine-valent HPV vaccine against 6-month persistent infection (PI) due to types 31, 33, 45, 52, and 58. Per protocol population

Endpoint 6-month PI	9vHPV No. cases/ total	qHPV No. cases/total	Efficacy (95% CI)
HPV 31	7/5251	150/5198	95.5% (90.7, 97.9)
HPV 33	1/5553	106/5560	99.1% (95.2, 100)
HPV 45	4/5649	124/5658	96.8% (92.1, 98.9)
HPV 52	11/5263	387/5160	97.3% (95.5, 98.7)
HPV 58	12/5297	225/5284	94.8% (91.0, 97.1)

The nine-valent vaccine was subsequently approved for use with a two-dose schedule at 0–6/12 months in girls and boys aged 9–14 years (► https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-2016-02.pdf)

15.7 Effectiveness of HPV Vaccines: From Trials to the Real World

Fourteen years after HPV vaccination was implemented in several countries, a considerable amount of disease impact data is available. HPV vaccination programs have been proven to reduce incident and prevalent HPV-related conditions and diseases even a couple of years after vaccination implementation. As those data come from ecological studies, results must be interpreted with care. Below, some of the available data on HPV vaccination effectiveness are reported.

The first diseases on which immunization have an impact are GWs.

In Australia, 5 years after implementation of HPV vaccination, a 93% reduction of GWs irrespective of vaccination status was registered in women aged <21 years and a 100% reduction in women who declared that they had been vaccinated. GW incidence in heterosexual men also decreased by indirect effect. Such an effect was not visible in the homosexual male population. In Denmark, after introduction of the vaccination program, the incidence ratio (IR) of GWs in 16- and 17-year-old women between 2008 and 2013 decreased from 1071 to 58 per 100,000 person-years and was reduced from 365 to 77 per 100,000 person-years in men.

Also, the prevalence of vaccine-type HPV DNA decreased significantly in Australian females aged 18–24 years: 4vHPV prevalence decreased from 29% to 7% in partially and to 2% in fully vaccinated women; a lower prevalence of vaccine-targeted types in unvaccinated women (19%) suggested herd immunity. Furthermore, in a country using the bivalent vaccine, such as Scotland, from a total of 4679 samples tested, a significant reduction in prevalence of HPV-16 and HPV-18 from 29.8% (95% CI 28.3, 31.3%) to 13.6% (95% CI 11.7, 15.8%) was registered in the 5 years after vaccination implementation.

Precancerous lesions have also decreased significantly following implementation of immunization strategies. Australian data updated to March 2014, with a vaccine coverage around 70% for three doses, showed a

reduction of high-grade precancerous lesions (CIN2/3) of 50% in women aged <21 years. In Scotland, a significant reduction of CIN diagnoses in women who received three doses of vaccine vs those not vaccinated was registered: for CIN 1, adjusted RR was 0.71 (95% CI 0.58–0.87; $P = 0.0008$). For CIN 2, adjusted RR was 0.5 (95% CI 0.4–0.63; $P = 0.0001$) and for CIN 3, adjusted RR was 0.45 (95% CI 0.35–0.58; $P = 0.0001$).

In 2020, first direct evidences collected in Sweden on the effectiveness of HPV vaccines against cervical cancer were published. Girls and women were evaluated for cervical cancer until their 31st birthday. Cervical cancer was diagnosed in 19 women who had received the quadrivalent HPV vaccine and in 538 women who had not received the vaccine. The cumulative incidence of cervical cancer was 47 cases per 100,000 persons among women who had been vaccinated and 94 cases per 100,000 persons among those who had not been vaccinated. After adjustment for age at follow-up, the incidence rate ratio for the comparison of the vaccinated population with the unvaccinated population was 0.51 (95% confidence interval [CI], 0.32–0.82). After additional adjustment for other covariates, the incidence rate ratio was 0.37 (95% CI, 0.21–0.57). After adjustment for all covariates, the incidence rate ratio was 0.12 (95% CI, 0.00–0.34) among women who had been vaccinated before the age of 17 years and 0.47 (95% CI, 0.27–0.75) among women who had been vaccinated at the age of 17–30 years.

Further data from 4 Nordic European countries (Denmark, Iceland, Norway, and Sweden) at the end of 14 years of follow-up after enrollment in FUTURE II were available in 2021. Young women (16–23 years of age) who received three qHPV vaccine doses during the randomized, double-blind, placebo-controlled FUTURE II base study were followed for effectiveness for an additional ≥10 years through national registries. The observed incidence of HPV-16/18-related high-grade cervical dysplasia was compared with recent historical background incidence rates in an unvaccinated population. No cases of HPV-16/18-related high-grade cervical dysplasia were observed in the per-protocol effectiveness population ($N = 2121$; 24,099·0 person-years of follow-up) during the entire study. Vaccine effectiveness of 100% (95% CI 94.7–100) was demonstrated for ≥12 years, with a trend toward continued protection through 14 years post-vaccination.

15.8 Safety of HPV Vaccines

All HPV vaccines showed a good safety profile in clinical trials. Local reactions (pain, swelling, induration, redness, etc.) are frequently reported side effects. Systemic reactions included fever, headache, vertigo, and nausea.

Post-marketing surveillance data include, as expected, reports of a wide range of adverse events following immunization (AEFIs). Causality assessment is a complex process that implies the verification of the simultaneous presence of different criteria, and not simply temporal association.

Several diseases of uncertain etiology have been reported after HPV vaccination; however, none of them was demonstrated to be causally associated with immunization.

For the quadrivalent vaccine, a review of 15 published post-marketing studies based on both passive and active surveillance showed an excellent record of safety on >1 million vaccinated subjects around the world. The US Institute of Medicine published a review on HPV vaccination, autoimmune disease, and acute disseminated encephalomyelitis (ADEM), which stated that the vaccine is not associated with an increased risk of multiple sclerosis or other demyelinating diseases.

The most recent threat to HPV vaccination programs was the report of some cases of complex regional pain syndrome (CRPS) and of postural orthostatic tachycardia syndrome (POTS) in vaccinated girls, following which vaccination coverage dramatically fell in Japan. Following a Danish request of review for evidence of possible causality, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency (EMA) stated that available evidence does not show any causal relationship between HPV vaccination and the two

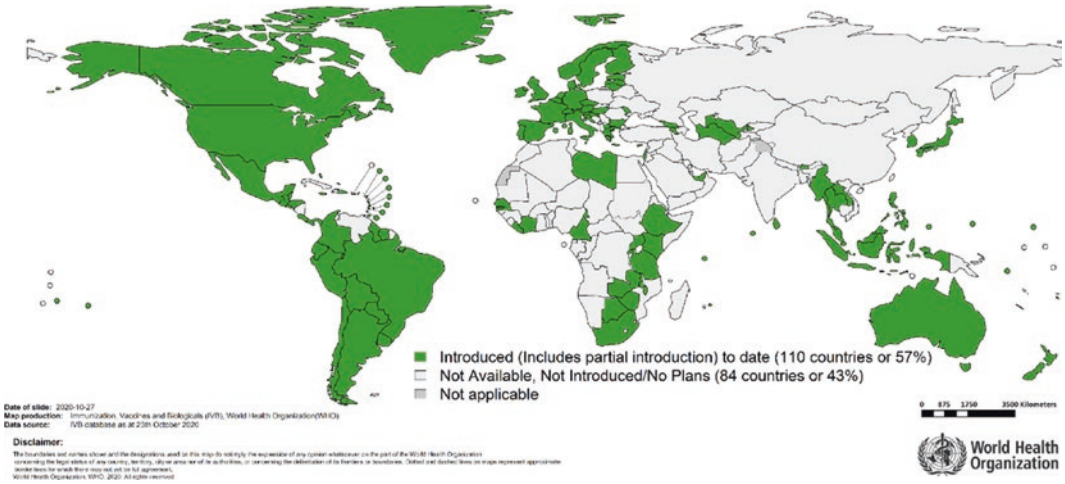


Fig. 15.1 Countries that include human papilloma virus (HPV) vaccine in their national immunization program. (Data source: WHO/IVB Database, as of 23rd October 2020. Map production Immunization Vaccines and Biologicals (IVB), World Health Organization; The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city, or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. ©WHO 2020. All rights reserved)

syndromes. Such a conclusion was endorsed officially by the EMA on November 20, 2015. In December 2015, the WHO Global Advisory Committee on Vaccine Safety confirmed that no such causal association exists, calling for efforts by Japan health authorities to restore vaccination coverage.

15.9 Vaccination Programs in the World

Vaccination for HPV has been recommended and implemented in the adolescent female population of several countries for about 14 years, starting from industrialized areas and achieving different coverage results (Fig. 15.1). In May 2018 the WHO Director-General made a global call for action toward the elimination of cervical cancer as a public health problem, aiming to reduce the annual incidence below 4 cases per 100,000 globally. In August 2020, the World Health Assembly passed a resolution calling for elimination of cervical cancer and adopting a strategy to make it happen.

Countries with limited resources have been involved in vaccination demonstration projects and, in some cases, have launched a national program with the help of international agencies and alliances (Fig. 15.2). Extension of the immunization offer to adolescent male subjects has become an important additional opportunity for several countries, also because the progressive decrease of vaccine costs and the possibility of administering two doses only in adolescents have made universal HPV immunization a cost-effective option in many instances. Special attention is needed for homosexual men with HIV infection, who are at a particularly increased risk for HPV-related diseases and deaths. However, it seems unlikely that a high vaccination coverage is reached in such a risk group, universal (female and male) adolescent programs being the real solution. An extension of female age groups involved in the active offer of immunization to include young adults would allow a faster impact of vaccination programs on HPV-related cancers and precancers.

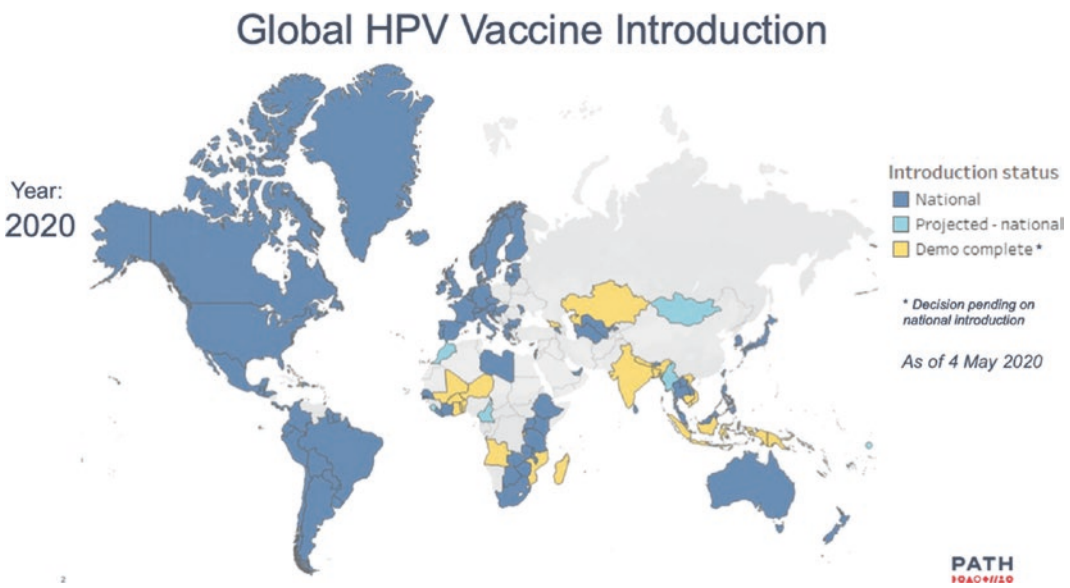


Fig. 15.2 Global HPV National Vaccine Introduction Projected National Introduction, and Completed Demonstration Projects as of May 4, 2020. (▶ https://path.azureedge.net/media/documents/Global_HPV_Vaccine_Intro_Overview_Slides_webversion_2020May.pdf)

Furthermore, it must not be forgotten that reaching high coverage with HPV vaccines can have a deep impact on the organization of screening programs. In the presence of a high coverage against HPV vaccine types in the population, it would be possible to extend HPV DNA testing as a primary screening test, and fewer screening rounds during a woman's lifetime would be sufficient to provide almost complete protection against HPV.

	Bivalent vaccine	Quadrivalent vaccine	Nonavalent vaccine
Antigens (virus-like particles – VLPs)	20 μg HPV-16 20 μg HPV-18	40 μg HPV-16 20 μg HPV-18 20 μg HPV-6 40 μg HPV-11	60 μg HPV-16 40 μg HPV-18 30 μg HPV-6 40 μg HPV-11 20 μg HPV-31 20 μg HPV-33 20 μg HPV-45 20 μg HPV-52 20 μg HPV-58
Expression system	Baculovirus expression vector system in *Trichoplusia ni* Rix4446 cell substrate	*Saccharomyces cerevisiae* yeast	*Saccharomyces cerevisiae* yeast
Adjuvant	AS04 Adjuvant system [50 μg MPL and 500 μg $Al(OH)^3$]	225 μg amorphous aluminum hydroxyphosphate sulfate	500 μg amorphous aluminum hydroxyphosphate sulfate
Administration schedule	2 doses 5–13 months apart from 9 to 14 years 3 doses at month 0, 1, 6 in subjects ≥15 years	2 doses at month 0 and 6 from 9 to 13 years 3 doses at month 0, 2, 6 in subjects ≥14 years	2 doses 5–13 months apart from 9 to 14 years 3 doses at month 0, 2, 6 in subjects ≥15 years

Further Reading

Ali H, Donovan B, Wand H, Read TR, Regan DG, Grulich AE, Fairley CK, Guy RJ. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. BMJ. 2013;346:f2032.

Bollerup S, Baldur-Felskov B, Blomberg M, Baandrup L, Dehlendorff C, Kjaer SK. Significant reduction in the incidence of genital warts in young men 5 years into the Danish Human Papillomavirus vaccination program for girls and women. Sex Transm Dis. 2016;43:238–42.

Bonanni P, Bechini A, Donato R, Capei R, Sacco C, Levi M, Boccalini S. Human papilloma virus vaccination: impact and recommendations across the world. Ther Adv Vaccines. 2015;3:3–12.

Bosch FX, Robles C, Díaz M, Arbyn M, Baussano I, Clavel C, et al. HPV-FASTER: broadening the scope for prevention of HPV-related cancer. Nat Rev Clin Oncol. 2016;13:119–32.

Brotherton JM, Saville AM, May CL, Chappell G, Gertig DM. Human papillomavirus vaccination is changing the epidemiology of high-grade cervical lesions in Australia. Cancer Causes Control. 2015;26:953–4.

Bruni L, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. Lancet Glob Health. 2016;4:e453–63.

Castellsagué X, Bosch FX, Muñoz N. Environmental co-factors in HPV carcinogenesis. Virus Res. 2002a;89:191–9.

Castellsagué X, Bosch FX, Muñoz N, Meijer CJ, Shah KV, de Sanjose S, et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. N Engl J Med. 2002b;346:1105–12.

De Flora S, Bonanni P. The prevention of infection-associated cancers. Carcinogenesis. 2011;32:787–95.

Dobson SR, McNeil S, Dionne M, Dawar M, Ogilvie G, Krajden M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. JAMA. 2013;309:1793–802.

Einstein MH, Baron M, Levin MJ, Chatterjee A, Edwards RP, Zepp F, et al. Comparison of the immunogenicity and safety of Cervarix and Gardasil Human Papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18-45 years. Hum Vaccin. 2009;5:705–19.

European Medicines Agency. Assessment report. Human Papilloma Virus (HPV) vaccines: 11 November 2015. http://www.who.int/vaccine_safety/committee/GACVS_HPV_statement_17Dec2015.pdf?ua=1.

FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356:1915–27.

Garland SM, Kjaer SK, Muñoz N, et al. Impact and effectiveness of the quadrivalent human papillomavirus vaccine: a systematic review of 10 years of real-world experience. Clin Infect Dis. 2016;63(4):519–27.

Hartwig S, Syrjänen S, Dominiak-Felden G, Brotons M, Castellsagué X. Estimation of the epidemiological burden of human papillomavirus-related cancers and non-malignant diseases in men in Europe: a review. BMC Cancer. 2012;12(3):30. doi: https://doi.org/10.1186/1471-2407-12-30.

Herweijer E, Sundström K, Ploner A, Uhnoo I, Sparén P, Arnheim-Dahlström L. Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: a population-based study. Int J Cancer. 2016;138:2867–74.

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Biological agents. IARC Monogr Eval Carcinog Risks Hum. 2010;100B. http://globocan.iarc.fr/old/FactSheets/cancers/cervix-new.asp.

ICO Information Centre on HPV and Cancer. Human papillomavirus and related diseases report – Europe. Available at: http://www.hpvcentre.net/statistics/reports/XEX.pdf. Accessed 30 January 2017.

Iversen OE, Miranda MJ, Ulied A, Soerdal T, Lazarus E, Chokephaibulkit K, et al. Immunogenicity of the 9-valent HPV vaccine using 2-dose regimens in girls and boys vs a 3-dose regimen in women. JAMA. 2016;316:2411–21.

Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015;372:711–23.

Kavanagh K, Pollock KG, Potts A, Love J, Cuschieri K, Cubie H, Robertson C, Donaghy M. Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely related HPV types. Br J Cancer. 2014;110(11):2804.

Kirnbauer R, Booy F, Cheng N, Lowy DR, Schiller JT. Papillomavirus L1 major capsid protein self-assembles into virus-like particles that are highly immunogenic. Proc Natl Acad Sci USA. 1992;89:12180–4.

Kjaer SK, Chackerian B, van den Brule AJ, Svare EI, Paull G, Walbomers JM, et al. High-risk human papillomavirus is sexually transmitted: evidence from a follow-up study of virgins starting sexual activity (intercourse). Cancer Epidemiol Biomark Prev. 2001;10:101–6.

Kjaer SK, Nygård M, Sundström K, Dillner J, Tryggvadottir L, Munk C, et al. Final analysis of a 14-year long-term follow-up study of the effective-

ness and immunogenicity of the quadrivalent human papillomavirus vaccine in women from four nordic countries. EClinicalMedicine. 2020 Jun 20;23:100401. doi: https://doi.org/10.1016/j.eclinm.2020.100401. eCollection 2020 Jun.

Launch of the Global Strategy to Accelerate the Elimination of Cervical Cancer. Available at: https://www.who.int/news-room/events/detail/2020/11/17/default-calendar/launch-of-the-global-strategy-to-accelerate-the-elimination-of-cervical-cancer

Lehtinen M, Paavonen J, Wheeler CM, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol. 2012;13:89–99.

Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, Sundström K, Dillner J, Sparén P. HPV Vaccination and the Risk of Invasive Cervical Cancer. N Engl J Med 2020; 383:1340−8.

Olsson SE, Villa LL, Costa RL, et al. Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine. Vaccine. 2007;25:4931–9.

Paavonen J, Jenkins D, Bosch FX, Naud P, Salmerón J, Wheeler CM, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. Lancet. 2007;369:2161–70.

Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer. 2006;118:3030–44.

Patel H, Wagner M, Singhal P, Kothari S. Systematic review of the incidence and prevalence of genital warts. BMC Infect Dis. 2013;13:39.

Pollock KG, Kavanagh K, Potts A, Love J, Cuschieri K, Cubie H, et al. Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland. Br J Cancer. 2014;111:1824–30.

Romanowski B, Schwarz TF, Ferguson LM, Peters K, Dionne M, Schulze K, et al. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared with the licensed 3-dose schedule: results from a randomized study. Hum Vaccin. 2011;7:1374–86.

Sinisgalli E, Bellini I, Indiani L, Sala A, Bechini A, Bonanni P, Boccalini S. HPV vaccination for boys? A systematic review of economic studies. Epidemiol Prev. 2015;39(Suppl 1):51–8.

Vichnin M, Bonanni P, Klein NP, Garland SM, Block SL, Kjaer SK, et al. An overview of quadrivalent human papillomavirus vaccine safety: 2006 to 2015. Pediatr Infect Dis J. 2015;34:983–91.

Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. Am J Epidemiol. 2003;157:218–26.

Tick-Borne Encephalitis Vaccines

Herwig Kollaritsch and Ulrich Heininger

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_16

16.1 Tick-Borne Encephalitis Disease

Tick-borne encephalitis (TBE) is caused by the TBE virus (TBEV), a member of the *Flavivirus* family. There are three antigenetically very closely related subtypes of the virus: the European subtype (TBEV-Eu), the Siberian subtype (TBEV-Sib), and the Far East subtype (TBEV-Fe). The virus is inoculated to the host by a sting (frequently and erroneously referred to as a "bite") from an infected tick and the virus then replicates locally, followed by viremia of 2–7 days and facultative invasion of the central nervous system.

Viremia occurs in all patients with TBEV infections, but approximately two-thirds of them remain asymptomatic and only one-third get clinical symptoms.

Tick-borne encephalitis is only rarely exported to other countries and a recent review on travel-associated TBE presented evidence that in 2012 only 39 cases of TBE were documented in Central and Western Europe among international travelers (Figs. 16.1 and 16.2).

Nevertheless, TBE has to be taken into account in the differential diagnosis of aseptic meningitis in patients who had stayed in a TBE-endemic area in the previous 4 weeks, especially in the warm season (▶ Box 16.1).

Box 16.1 Criteria for Tick-Borne Encephalitis (TBE) Case Confirmation and Consecutive Case Classification

Clinical criteria

Any person with symptoms of inflammation of the central nervous system (e.g., meningitis, meningoencephalitis, encephalomyelitis, encephaloradiculitis).

Laboratory criteria[1]

1. Confirmed case:
   At least one of the following five:
   - TBE-specific immunoglobulin M (IgM) and immunoglobulin G antibodies in blood
   - TBE-specific IgM antibodies in cerebrospinal fluid
   - Seroconversion or fourfold increase in TBE-specific antibodies in paired serum samples
   - Detection of TBE viral nucleic acid in a clinical specimen
   - Isolation of the TBE virus from a clinical specimen
2. Probable case:
   - Detection of TBE-specific IgM antibodies in a unique serum sample

Epidemiological criteria

- Exposure to a common source (unpasteurized dairy products)

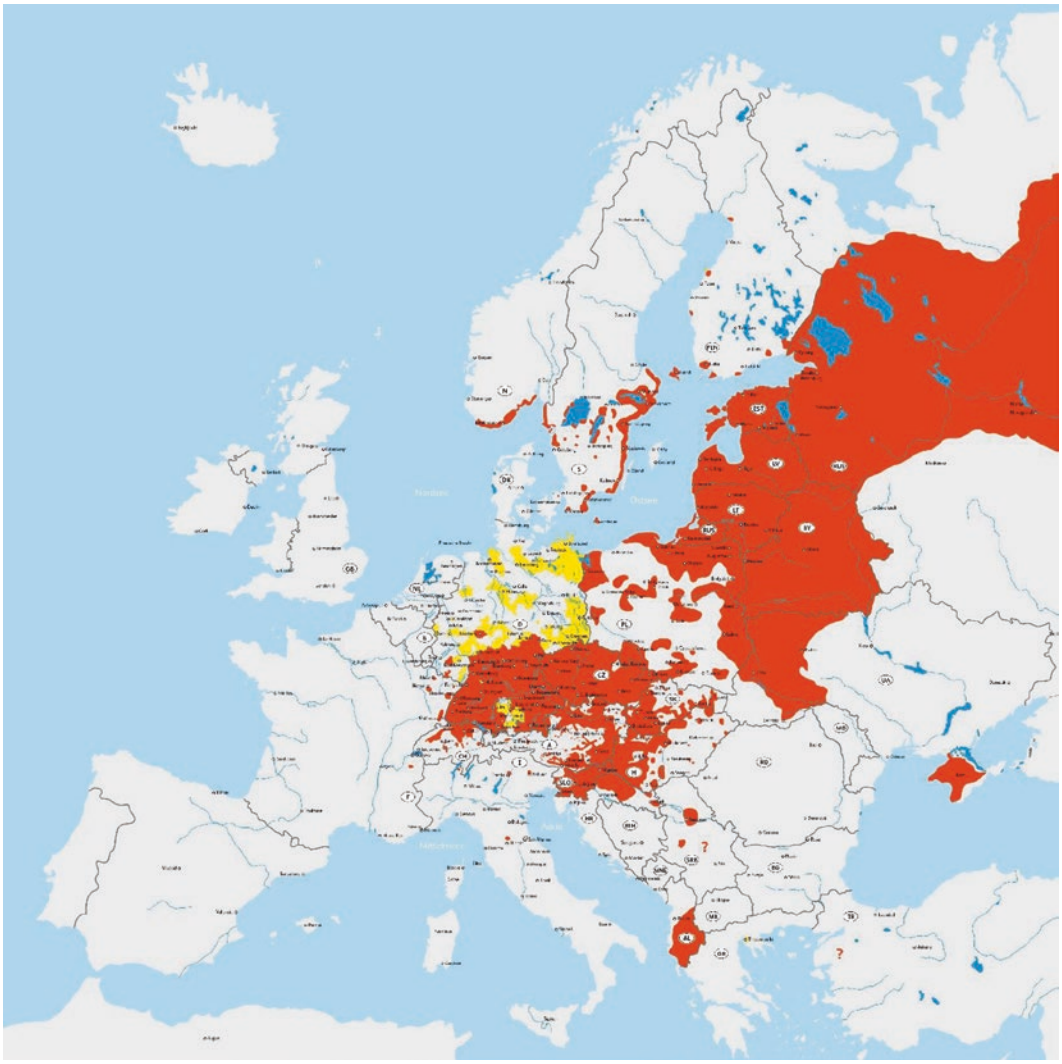
Case classification

(i) *Possible case:* not applicable

(ii) *Probable case*
- Any person meeting the clinical criteria and the laboratory criteria for a probable case, or
- Any person meeting the clinical criteria and with an epidemiological link

(iii) *Confirmed case*
- Any person meeting the clinical and laboratory criteria for case confirmation

1 Serological results should be interpreted according to the vaccination status and previous exposure to other flaviviral infections. Confirmed cases in such situations should be validated by serum neutralization assay or other equivalent assays.



Known TBE risk areas as of 2015

Areas considered to be endemic without precise documentation

Areas with solitary cases of TBE

Fig. 16.1 Endemic areas of tick-borne encephalitis (TBE) in Europe. (©Pfizer with permission)

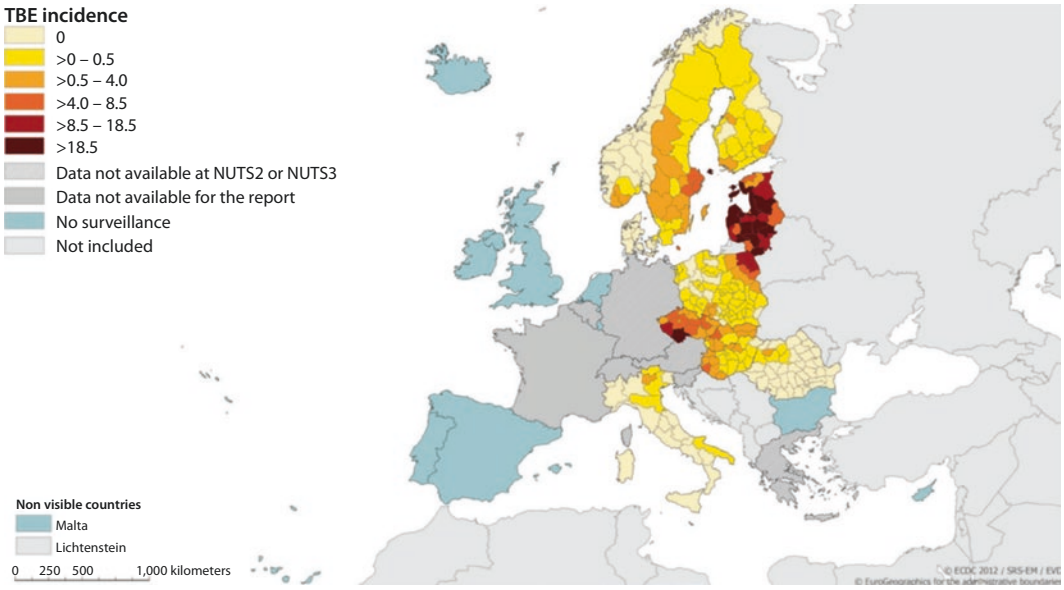


Fig. 16.2 The average annual incidence rate of TBE per 100,000 inhabitants in the EU/European Free Trade Association area at a lower administrative-level Nomenclature of Territorial Units for Statistics (NUTS) 2 (Italy) or NUTS 3. (European Centre for Disease Prevention and Control 2012)

16.2 TBE Vaccines

16.2.1 Vaccines

Currently, four different inactivated whole-virus alum-adjuvanted vaccines against TBE are available, two of them regionally in Russia (based on TBEV-Sib) and two in Europe (based on TBEV-Eu). The two European vaccines, Encepur® (available since 1994) and FSME-Immun® (available since 1976) are formulated in two separate preparations: one for children and one for adults. Both vaccine brands underwent a series of modifications up to the beginning of the millennium, when the actual preparations (Table 16.1) were introduced to the market. FSME-Immun 0.25 ml junior® is licensed for use in children ≥1–15 years of age. It contains 1.2 mcg of inactivated TBEV-Eu strain Neudörfl. Encepur 0.25 ml children® is licensed according to the Summary of Product Characteristics for children ≥1–11 years of age and contains 0.75 mcg inactivated TBE virus strain Karlsruhe 23. The respective virus strains are cultivated on primary chicken embryonic cells. The vaccines contain either sucrose (Encepur®) or human serum albumin (HSA; FSME-Immun®) as stabilizers, both without any preservative (Table 16.1).

Adult formulations of the TBE vaccines simply contain twice the amount of antigen of the respective vaccines for children in 0.5 ml volume and should be used for intramuscular administration in individuals 12 (Encepur®) and 16 years of age (FSME-Immun®) onward respectively.

16.2.2 Immunization Schedules

The conventional basic immunization schedule of TBE vaccines consists of two doses given at an interval of 1–3 months, followed by a third dose 5 or 9–12 months later, ideally applied before the tick season starts. The first booster dose should be applied 3 years later and then boosting is recommended in 5-year intervals to maintain circulating neutralizing antibodies. Some national recommendations differ from this licensed schedule, for example, the Austrian authorities recommend a 3-year booster interval for persons ≥60 years of age and in Switzerland booster doses are recommended at intervals of 10 years.

Table 16.1 Specific characteristics and composition of European tick-borne encephalitis (TBE) vaccines

Name and producer	FSME-IMMUN®; Pfizer	Encepur®; GSK
Antigen details		
Strain	TBEV-Eu Neudörfl	TBEV-Eu K23
Passages	PCEC	PCEC
Production	PCEC	PCEC
Amount of antigen (adults/children)	2.4 µg/1.2 µg	1.5 µg/0.75 µg
Excipients		
Adjuvant	$Al(OH)_3$	$Al(OH)_3$
Preservative	No	No
Stabilizer	HSA	Sucrose
Presentation		
Formulation (adults/children)	0.5/0.25 ml, liquid	0.5/0.25 ml, liquid
Packaging	Prefilled syringe	Prefilled syringe
Shelf life	30 months (2–8 °C)	30 months (2–8 °C)

Adapted from WHO (2011)
TBEV-Eu tick-borne encephalitis virus European strain, *HSA* human serum albumin, *PCEC* primary chicken embryonic cells, $Al(OH)_3$ aluminum hydroxide

For both vaccines, accelerated immunization schedules are licensed, consisting of a series of three doses on days 0–7–21, followed by a fourth dose after 12–18 months (Encepur®) and two doses 14 days apart with a third dose after 5–12 months (FSME-Immun®; Table 16.2).

16.2.3 Irregular Vaccination Schedules

If a person has received only one dose of TBE vaccine, a second dose should be applied within 1 year after the first one; otherwise, immune response is not guaranteed (seroconversion 94% rather than >95%). After at least two doses, a single further dose administered up to 20 years (and beyond) later leads to a sufficient anamnestic response, indicating a robust immune memory.

16.2.4 Interchangeability

FSME-Immun® and Encepur® can be administered alternately for boosting, whereas the primary series (at least doses 1 and 2) should be performed with either product, as data on interchangeability during basic immunization are scarce.

16.2.5 TBE Vaccination After a Tick Sting

There are no generally accepted postexposure procedures in persons without or with incomplete immunizations against TBE in the case of a tick sting in a TBE-endemic area. However, the Austrian Health Authorities published a useful schedule in their national vaccination recommendations (Table 16.3) that may be followed. Basically, a first dose of

Table 16.2 Immunization schedules for TBE vaccines[a] according to the Summary of Product Characteristics, intervals given in months unless indicated otherwise

	Basic immunization conventional schedule; (dose 1 on day 0)		Basic immunization rapid schedule; (dose 1 on day 0)			First booster (years)	Subsequent boosters (years)
	2nd dose (months)	3rd dose (months)	2nd dose	3rd dose (months)	4th dose (months)		
FSME-Immun®	1–3	5–12	14 days	5–12	–	3	5[b]
Encepur®	1–3	9–12	7 days	21 days	12–18[c,d]	3	5[b]

Adapted from WHO (2011)

[a]Schedules apply for both preparations (children's and adults' preparation)

[b]In persons 50 years of age and older, an interval of 3 years (Austria: persons 60 years of age and older); Switzerland: 10-year intervals, independent of age

[c]Considered as first booster

[d]Alternatively, as with FSME-Immun®, the interval between the first doses may be reduced to 14 days, followed by a third dose 9–12 months later

Table 16.3 TBE vaccination after a tick sting

Vaccination history (written documentation)	Interval between last immunization and tick sting	Interval between tick sting and physician visit[a]	Recommendation
Unvaccinated or unknown	Not applicable	<4 weeks	Wait until ≥4 weeks after sting, then initiate immunization series
1 dose	≤14 days	Not relevant	Wait until ≥4 weeks after sting, then administer second dose
	15 days–1 year	<48 h	Administer second dose immediately
		≥48 h	Wait until ≥4 weeks after sting, then administer second dose [b]
	≥1 year	<48 h	Administer second dose immediately[b]
		≥48 h	Wait until ≥4 weeks after sting, then administer second dose[b]
≥ 2			Additional vaccination according to regular schedule

Adapted from BMG (2016)

[a]If time elapsed is not to be determined, use schedule ">48 h after tick sting"

[b]Control of antibody response recommended. If not possible, count this vaccination as the first one in the basic immunization schedule

immunization should be avoided in a previously unimmunized patient during the TBE incubation period after a tick sting, as it is not expected to be efficient, but may cause concern if it interferes with natural TBE infection.

16.3 TBE Vaccines: Immunogenicity and Effectiveness

16.3.1 Immunogenicity

Encepur® and FSME-Immun® have been registered based on immunogenicity and safety study data, but no controlled trials with clinical efficacy endpoints have been conducted. For both vaccines, ample data on their immunogenicity are available, demonstrating high seroconversion rates of close to 100% and robust neutralizing antibody titers in healthy subjects. Persistence of neutralizing antibodies after primary and/or booster vaccinations indicate long-term protection in healthy persons. Of note, age at initiation of the immunization series plays an important role, with higher seroconversion rates and mean antibody values in addition to more prolonged antibody persistence in children and adolescents compared with adults.

Focusing on the pediatric use of the two TBE vaccines, a number of studies have evaluated the immunogenicity of the preparations and consistently found high seroconversion rates of 98–100% after a primary course (conventional or accelerated dosing schedule) of vaccinations and appropriate persistence of neutralizing antibodies to support the recommended boosting intervals. A few studies show evidence that antibody persistence in children may be even longer than expected. There is no convincing evidence that one vaccine would induce a superior immune response or lead to better protection against disease than the other.

16.3.2 Cross-Protection

TBEV-Eu-containing vaccines induce some cross-protection against the other TBEV subtypes, indicating that FSME-Immun® and Encepur® are also protective against TBEV-Sib and TBEV-Fe.

16.3.3 Immunocompromised Patients and Low Responders

The TBE vaccines induce a strong and robust immune memory in healthy persons. However, there is some recent evidence that in immunocompromised patients or those with certain underlying chronic diseases the immune response may be impaired. Primary low responsiveness after vaccination seems to occur rarely: Recent investigations of "low responders" after TBE vaccination show that low cellular, humoral, and cytokine response levels, particularly IL-2 and IFN-γ, correlate with each other. Although immune response may be impaired, there is consensus that TBE vaccination with the available vaccines will do no harm in immunocompromised patients.

16.3.4 Field Effectiveness

Field effectiveness of TBE vaccines has been investigated systematically in Austria, where vaccination coverage reached a sufficient level to obtain robust data. A first calculation, covering the period 2000–2006, yielded a field effectiveness of 99% for regularly vaccinated (mainly with FSME-Immun®) persons and reached 95.5% for those with irregular immunization schedules. A further analysis covering the years 2010–2011 (including approximately one third of subjects vaccinated with Encepur®) showed similar results: Effectiveness was 98.7% for regularly vaccinated subjects and 92.5% in those with irregu-

Table 16.4 Safety and reactogenicity of Encepur® and FSME-Immun® (Source: SPC)

Vaccines and probability of occurrence (adverse events/doses)	≥1/10	≥1/100 <1/10	≥1/1000 <1/100	≥1/10,000 <1/1000	Not known (based on single cases or small case series)
FSME-Immun ® First dose: *n* = 3512 Second dose: *n* = 3477 Third dose: *n* = 3277	Local reaction at injection site: Redness, swelling, induration	Headache, nausea Myalgia, arthralgia Malaise, fatigue	Lymphadenopathy Vertigo Vomiting Fever (only exceptionally >39 °C)	Acute allergic reactions Somnolence Diarrhea, abdominal pain	Aggravation of autoimmune disease Visual impairment, photophobia, meningismus, epilepsy, encephalitis, neuritis, tachycardia Urticaria, pruritus, exanthema Flu-like symptoms, weakness, edema
Encepur ® (pooled date from clinical studies and postmarketing surveillance)	Transient pain at injection site; general malaise, myalgia Headache	Redness, swelling at injection site Flu-like symptoms Nausea, arthralgia	Arthralgia and myalgia (neck)	Granuloma at injection site Lymphadenopathy Neuritis-like symptoms Diarrhea Systemic allergic reactions such as urticaria, dyspnea, bronchospasm, hypotension	Extremely rare: Guillain–Barré syndrome

lar schedules, respectively. These data are in accordance with only few reports of vaccine failure in fully vaccinated individuals during the last few decades.

It is estimated that in Austria around 4000 cases of TBE were prevented by vaccination between 2000 and 2011 and the yearly reported number of TBE cases fell to 10–15% compared with the pre-vaccination era levels.

16.4 TBE Vaccines: Adverse Events and Contraindications

16.4.1 Reactogenicity

The formulations of the TBE vaccines have been refined several times over the past decades and this has significantly reduced their reactogenicity. WHO and Cochrane reviews on safety attested the two TBEV-Eu–based vaccines to be safe. Pharmacovigilance data from both manufacturers, including about 72 million doses of vaccines of both brands distributed from 2001 to 2009, indicate a combined rate of severe adverse events of 1.6–1.9 per 100,000 doses. These include a range of entities, usually coinciding with immunization, but not necessarily causally related.

Typical systemic adverse events in children include mild and short-lasting fever mainly associated with the first dose and with a very low frequency of less than 0.5% (medically accompanied cases) of vaccinated individuals in a cohort of more than 25,000 vaccinees. Other systemic adverse events include headache, fatigue, malaise, muscle pain, and joint pain. Local redness, injection site pain, and itching may also occur. For details see Table 16.4. Allergic reactions to vaccine components occur only occasionally.

16.4.2 Contraindications

The TBE vaccines are contraindicated in persons with acute diseases. Allergies to vaccine components also constitute contraindications; in the case of egg protein allergy, contraindication is restricted to severe forms, that is, with anaphylactic reactions. In all other patients, appropriate precautionary measures and supervision after immunization should be applied. Chronic diseases, including those affecting the central nervous system, are not a contraindication for TBE vaccination. However, the phenomenon of coinciding changes in the natural course of such underlying diseases should be discussed with the patients or their parents before immunization.

16.5 TBE Vaccination Recommendations

With more than 30 years of experience with the use of TBE vaccines in Europe, there is ample evidence for their positive public health impact. Most European countries, especially those with endemic TBE areas, do recommend TBE vaccination for their populations at risk, including travelers to endemic areas outside the country. In accordance with the labeled licensure of the vaccines, this includes children 1 year of age or older. In contrast, Austria is the only European country to date with a universal vaccination recommendation, reflecting the high burden of TBE in the pre-immunization era and the wide distribution of endemic areas in that country. The current recommendations for selected European countries are listed in Table 16.5.

In addition, there is a tendency in Europe to limit vaccination recommendations to older age groups, as pediatric TBE cases tend to be less severe, although there is growing evidence that TBE cases in children may also take a severe clinical course and long-term outcome after TBE in children is underestimated. Cost–benefit calculations of TBE vaccination for endemic areas is mostly not available; only one study predicted savings of $80million for Austria from a general vaccination recommendation. More recent data from Slovenia clearly indicated the cost-effectiveness of TBE vaccination for a highly endemic country.

Table 16.5 Vaccination recommendation for TBE

Country	Recommendation status
Albania	No policy
Austria	Universal recommendation ≥1 year of age
Bulgaria	No policy
Croatia	For highly endemic areas and occupational exposure
Czech Republic	For highly endemic areas and occupational exposure
Estonia	Recommended for populations at risk[a]
Finland	Recommended for endemic areas
Germany	Recommended for endemic areas
Hungary	Recommended for populations at risk[a]
Italy	Recommended on a district level
Latvia	Recommended for populations at risk[a]
Lithuania	Recommended for populations at risk[a]
Norway	Recommended for high-risk populations
Poland	Recommended for high-risk populations
Romania	No policy
Serbia	No policy
Slovakia	For highly endemic areas and occupational exposure
Slovenia	For highly endemic areas and occupational exposure
Sweden	Recommended for highly and moderately endemic districts, above 1 or 3 years of age respectively
Switzerland	Recommended for individuals living in or travelling to endemic areas, in general ≥6 years of age

Adapted from Hombach et al. (2016)
No detailed specifications available

Further Reading

BMG. Nationaler Impfplan der Republik Österreich. Bundesministerium für Gesundheit, 2016. http://bmg.gv.at/cms/home/attachments/2/8/1/CH1100/CMS1452867487477/impfplan.pdf.

Cizman M, et al. Severe forms of tick-borne encephalitis in children. Wien Klin Wochenschr. 1999;111(12):484–7.

Demicheli V, Debalini MG, Rivetti A. Vaccines for preventing tick-borne encephalitis. Cochrane Database Syst Rev. 2009(1):CD000977.

ECDC. Epidemiological situation of tick-borne encephalitis in the European Union and European Free Trade Association countries. ECDC: Stockholm; 2012.

Fowler A, et al. Biomarkers in cerebrospinal fluid of children with tick-borne encephalitis. Pediatr Infect Dis J. 2016;35(9):961–6. doi: https://doi.org/10.1097/INF.0000000000001210.

Heinz FX, et al. Vaccination and tick-borne encephalitis, central Europe. Emerg Infect Dis. 2013;19(1):69–76.

Kaiser R. Tick-borne encephalitis. Infect Dis Clin N Am. 2008;22(3):561–75.

Kollaritsch H, et al. Vaccines and vaccination against tick-borne encephalitis. Expert Rev. Vaccines. 2012;11(9):1103–19.

Lindquist L. Tick-borne encephalitis. Handb Clin Neurol. 2014;123:531–59.

Loew-Baselli A, et al. Prevention of tick-borne encephalitis by FSME-IMMUN® vaccines: review of a clinical development programme. Vaccine. 2011;29:7307–19.

Orlinger KK, et al. A tick-borne encephalitis virus vaccine based on the European prototype strain induces broadly reactive cross-neutralizing antibodies in humans. J Infect Dis. 2011;203(11):1556–64.

Paulke-Korinek M, et al. Factors associated with seroimmunity against tick borne encephalitis virus 10 years after booster vaccination. Vaccine. 2013;31(9):1293–7.

Plotkin, SA, Orenstein, W, Offit, PA, Edwards, KM. Plotkin's Vaccines. seventh Edition. Philadelphia, PA: Elsevier; 2017

Pollabauer EM, et al. Clinical evaluation to determine the appropriate paediatric formulation of a tick-borne encephalitis vaccine. Vaccine. 2010a;28(29):4558–65. doi: https://doi.org/10.1016/j.vaccine.2010.04.075.

Pollabauer EM, et al. Comparison of immunogenicity and safety between two paediatric TBE vaccines. Vaccine. 2010b;28(29):4680–5. doi: https://doi.org/10.1016/j.vaccine.2010.04.047.

Prymula R, et al. Antibody persistence after two vaccinations with either FSME-IMMUN® Junior or ENCE®(R) Children followed by third vaccination with FSME®MUN(R) Junior. Hum Vaccin Immunother. 2012;8(6):736–42.

Schosser R, et al. Irregular tick-borne encephalitis vaccination schedules: the effect of a single catch-up vaccination with FSME-IMMUN. A prospective non-interventional study. Vaccine. 2014;32(20):2375–81.

Schuler M, et al. Epidemiology of tick-borne encephalitis in Switzerland, 2005 to 2011. Euro Surveill. 2014;19(13):pii: 20756.

WHO. Vaccines against tick-borne encephalitis. WHO position paper. WER. 2011;24(86):241–56.

Wittermann C, Petri E, Zent O. Long-term persistence of tick-borne encephalitis antibodies in children 5 years after first booster vaccination with Encepur Children. Vaccine. 2009a;27(10):1585–8.

Wittermann C, Schondorf I, Gniel D. Antibody response following administration of two paediatric tick-borne encephalitis vaccines using two different vaccination schedules. Vaccine. 2009b;27(10)1661–6.

Zent O, et al. Safety, immunogenicity and tolerability of a new pediatric Tick-Borne Encephalitis (TBE) vaccine, free of protein-derived stabilizer. Vaccine. 2003;21(25–26):3584–92.

Bacterial Vaccines and Vaccination

Contents

Tuberculosis Vaccines

Federico Martinón-Torres and Carlos Martín

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_17

17.1 Introduction

Despite all the efforts to fight it since the discovery of *Mycobacterium tuberculosis* by Robert Koch in 1882, tuberculosis (TB) it is still responsible for nearly 1.4 million deaths per year worldwide.

TB is primarily a pulmonary disease caused by *M. tuberculosis* and transmitted via the respiratory route, which could present different manifestations and affect bones, the central nervous system, and lymph nodes, and the progression of the disease can have several outcomes, largely determined by the response of the host immune system. TB is a major contributor to mortality in under 5-year-olds in TB-endemic settings.

Bacillus Calmette–Guérin (BCG) is the current vaccine against TB. BCG provides a strong protection against disseminated forms of the disease in infants and young children, but confers very limited protection against pulmonary forms of TB, which are responsible for the transmission of the disease. Today, BCG is included in the immunization schedule for TB-endemic countries, with a global coverage at birth close to 90% worldwide. In Europe, most of the countries in the past exercised BCG vaccination policy for all and currently recommend BCG vaccination for special groups (for information concerning country's BCG policies and practices visit ► http://www.bcgatlas.org/ and for Europe ► http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx).

The goals of the World Health Organization's (WHO) 2015 End TB Strategy include a 95% reduction in TB deaths and a 90% global disease reduction by 2035; for this, it is necessary to develop a comprehensive and appropriate approach that includes new and more effective vaccines, in addition to improved diagnostics and treatment.

17.2 Tuberculosis Epidemiology

In 2020, the WHO estimated that out of the ten million people developed TB in 2019, of which children aged <15 years accounted for 12%, and a total of 1.4 million people died from TB including with HIV coinfection. Geographically, most people who developed TB in 2019 were in the WHO regions of Southeast Asia (44%), Africa (25%), and the Western Pacific (18%). Eight countries accounted for two-thirds of the global total: India (26%), Indonesia (8.5%), China (8.4%), the Philippines (6.0%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%), and South Africa (3.6%) (◘ Fig. 17.1). Global total of 206,030 people with MDR/RR-TB were detected and notified in 2019, a 10% increase from 186.883 in 2018 {WHO:2020vz}. The year 2018 saw a further decrease in TB, with 259,000 incident TB cases (225,000–296,000) estimated in the WHO European Region, corresponding to 28 cases per 100,000 population according to European Centre for Disease Control (ECDC), and the WHO reported on the TB situation according to 2020 data (◘ Fig. 17.2). In 2018, there were an estimated 77,000 new cases of rifampicin-resistant and multidrug-resistant TB (RR/MDR TB) in the Region.

17.3 BCG Vaccine

The BCG vaccine is currently the only licensed vaccine against TB in use today, and is one of the most widely administered vaccines in the world. Around 4 billion BCG doses have been administered worldwide in history, principally in the setting of routine newborn immunization (as recommended by the WHO). Today, global immunization BCG coverage at birth is estimated to be close to 90% (◘ Fig. 17.3).

The original strain of *Mycobacterium bovis* BCG strain was developed in 1921 in France at the Pasteur Institute with attenuation through serial passage of an isolate from a cow with TB mastitis. This isolate was subsequently distributed to several laboratories in the world and a number of strains developed. Before the adoption of freeze-drying in the 1960s, the different laboratories preserved their strain by repeated subculture passages, and this resulted in the appearance of different BCG sub-strains that became designated

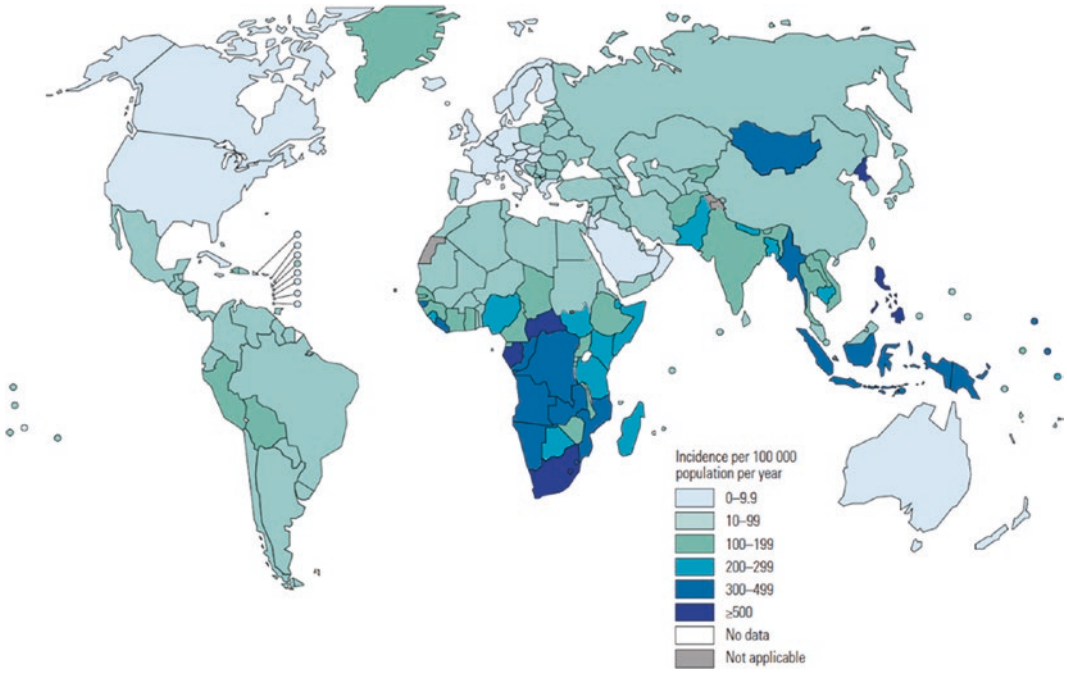


Fig. 17.1 Worldwide tuberculosis data estimated tuberculosis cases (any form) incidence rates 2019 per 100,000 population. (WHO report 2020)

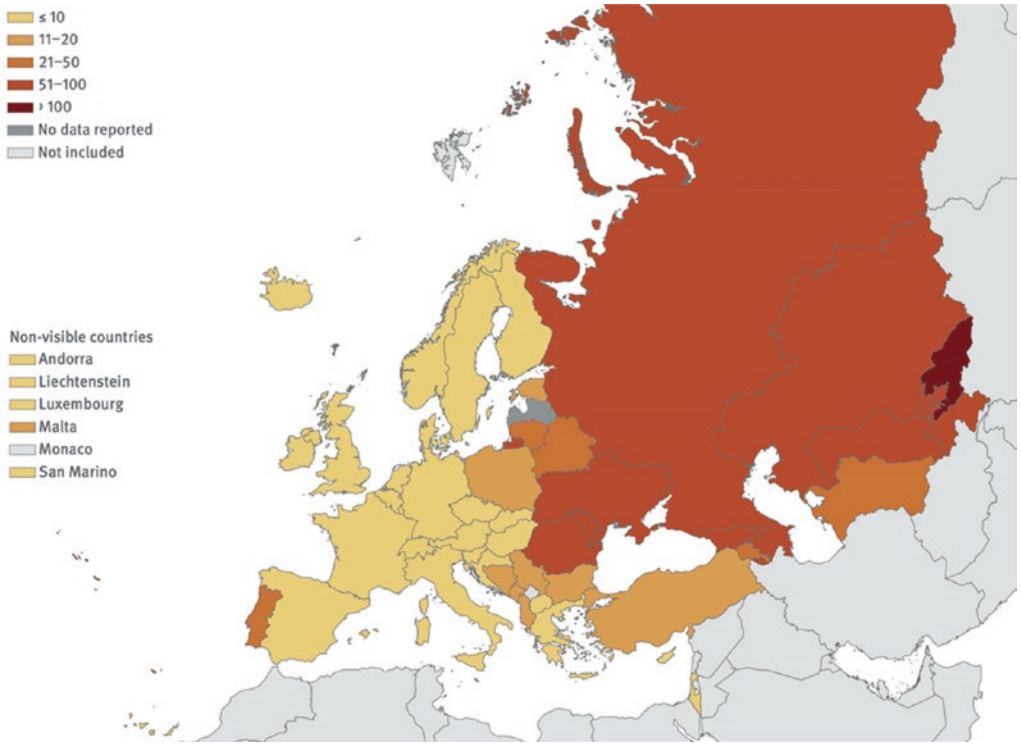


Fig. 17.2 Tuberculosis notification rates of new tuberculosis cases and relapses per 100,000 population, European Region, 2018. (From 2020 WHO/ECDC TB report)

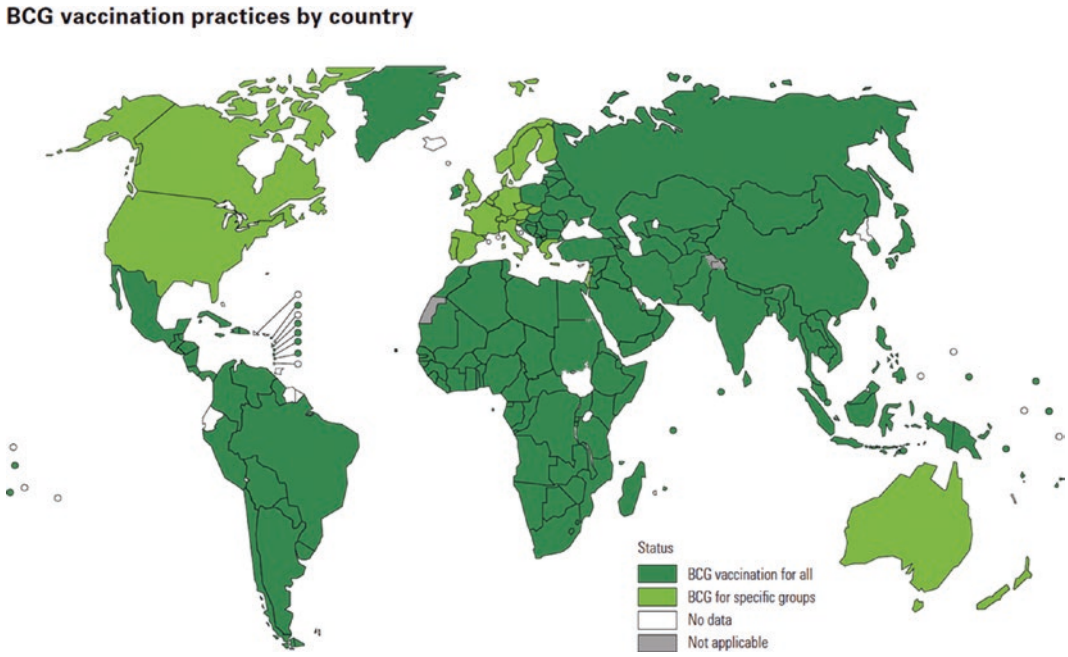


Fig. 17.3 Map of the BCG vaccination practices by country. (WHO TB Report 2020) (Source: The BCG World Atlas, second Edition, ► http://www.bcgatlas.org/, acces August 2020)

by the laboratory. Genomic analysis of BCG strains has documented multiple molecular changes. The main reason for BCG attenuation is the loss of the region of difference 1 (RD1). RD1 region is associated with subsequent loss of the immunodominant virulence factor, the early secretory antigen of 6 kDa (ESAT-6) and CFP10, both antigens used in that interferon-γ release assay (IGRA), to differentiate BCG vaccination from *M. tuberculosis* infection. Multiple other deletions probably contribute to phenotypic differences between BCG strains and although there are clear reactogenicity differences, it is not clear whether strain differences are a significant factor contributing to the variable efficacy of BCG observed in clinic.

Currently, five main BCG strains account for more than 90% of the vaccines in use worldwide in international immunization programs, each strain possessing different characteristics. The agreed terminology for the strains includes the Pasteur 1173 P2, the Danish 1331, the Glaxo 1077 (derived from the Danish strain), the Tokyo 172–1, the Russian BCG-I, and the Brazil Moreau RDJ. BCG vaccine shortages have been reported in many countries. These shortages started in 2013 and continued into 2015. The United Nations Children's Fund (UNICEF) is the main supplier of BCG vaccine to TB-endemic countries. Two of its four suppliers, the Statens Serum Institut in Denmark and the Serum Institute of India experienced technical difficulties that resulted in reduced production capacity. Global demand for BCG is estimated at 260 million doses per year. UNICEF reported shortages of eight million doses in 2013, of 23 million doses in 2014, and of 17 million doses in 2015.

The BCG vaccine is administered intradermally, after reconstitution of a lyophilized composition. After reconstitution, every 1 ml of vaccine contains ten doses 2–8 × 10^5 cfu of *M. bovis* live attenuated BCG (0.1 ml of the reconstituted vaccine). The vaccine should be stored between 2 ° C and 8 ° C. When reconstituted it should be protected from light.

Vaccine dosage:

- For adults and children >12 months, 0.1 ml of the reconstituted vaccine is recommended.
- For infants <12 months, 0.05 ml of the reconstituted vaccine is recommended.

Currently, there are new vaccines against TB under development, some of which are designed to boost the effects of BCG and others as BCG replacement vaccines (see further).

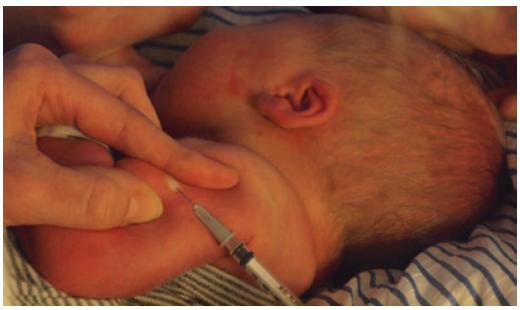
17.4 Methods of Administration

The injection site should be dry and clean. If the skin is swabbed with an antiseptic (such as alcohol), this should be allowed to evaporate completely before the injection is given.

The BCG vaccine should be administered by personnel trained in the intradermal technique, using a syringe of 1 ml sub-graduated into hundredths of a milliliter (1/100 ml), fitted with a short bevel needle (25G/0.50 mm or 26G/0.45 mm). Jet injections or multiple puncture devices should not be used.

The vaccine should be injected strictly intradermally in the arm, over the distal insertion of the deltoid muscle onto the humerus (approximately one-third down the upper arm) as follows (◘ Fig. 17.4):

- The skin is stretched between thumb and forefinger.
- The needle should be almost parallel to the skin surface and slowly inserted (bevel upward), approximately 2 mm into the superficial layers of the dermis.
- The needle should be visible through the epidermis during insertion.
- The injection is given slowly.
- A raised, blanched bleb is a sign of correct injection.



◘ **Fig. 17.4** Administration of the BCG vaccine. The skin is stretched between thumb and forefinger. The needle should be almost parallel with the skin surface and slowly inserted (bevel upward), approximately 2 mm into the superficial layers of the dermis. The needle should be visible through the epidermis during insertion. The injection is given slowly. A raised, blanched bleb is a sign of correct injection. (Picture courtesy of Dr. Jesper Kjærgaard, Copenhagen University Hospital)

The injection site is best left uncovered to facilitate healing.

17.5 Efficacy of BCG

The efficacy of the current TB vaccine BCG is consistent against the severe forms of the disease (meningeal and miliary TB), but is limited against pulmonary forms of the disease; this disease manifestation is responsible for transmission – fueling the growing epidemic worldwide. The most controversial aspect of BCG is its variable efficacy when used in different trials, with variable, geographically dependent, efficacy against pulmonary TB. BCG does not seem to protect against disease when given to people already infected or sensitized to environmental mycobacteria, which could explain the geographic variation. Furthermore, until recently, it was not possible to establish whether the protective effect of BCG vaccination against disease stemmed from its action in preventing acquisition of infection or limited to the prevention of progression from infection to clinical disease. A systematic review and meta-analysis conducted in 2014 demonstrated that the BCG vaccine reduced infections by 19–27% and progression to active TB by 71%.

Primary vaccination of newborns and infants appears to confer better protection than older children and adults. The absence of prior *M. tuberculosis* infection or sensitization with environmental mycobacteria is associated with higher efficacy of BCG against pulmonary TB and possibly against miliary and meningeal TBs. In contrast, the immune response to mycobacterial antigens in older children and adults living in areas that are endemic for TB appear to have higher background immunity than those living in non-endemic areas. This could have an influence on the relative efficacy of BCG when admin-

istered to older children and adults living in TB-endemic regions.

The possible reasons for variable efficacy include:

- Genetic variability of the population.
- Environmental factors as suggested by the relatively good efficacy seen in temperate regions compared with tropical regions of the globe.
- Background exposure to the disease TB: Previous exposure may both limit the replication of BCG ("blocking") and/or confer protection equivalent to BCG ("masking").
- Nonspecific immune responses against TB mycobacteria by non-TB mycobacteria.
- Exposure to parasites that skew the immune response toward a Th2 type of response rather than a Th1 type of response, the latter believed to be most important for immunoprotection.
- The use of different strains of BCG with potentially different efficacy. However, a recent meta-analysis of trials, including 18 studies reporting on protection against pulmonary and six reporting on protection against miliary or meningeal tuberculosis, showed no evidence that the efficacy of BCG was influenced by vaccine strains.

17.6 Immune Response to BCG

The immune response to primary BCG immunization has been evaluated in different studies in children demonstrating that there is a BCG-associated induction of $CD4^+$ and $CD8^+$ T cells, interferon (IFN)-γ a^+, interleukin (IL)-2^+, tumor necrosis factor (TNF)-α^+, and polyfunctional $CD4^+$ T cells.

As there is a lack of correlate of protection for TB, immunological studies of infant BCG immunization cannot currently be applied to determine immunization policy because a surrogate marker of BCG-induced protection is yet to be identified.

The BCG vaccine is administered intradermally. As natural infection and sensitization to *M. tuberculosis* in humans usually occur via the respiratory route, research is being conducted on the respiratory administration of BCG as we will discuss later in this chapter.

17.7 Heterologous Protection Including COVID-19

The BCG vaccination reduces rates of *M. tuberculosis* infection and provides strong protection against disseminated forms of the disease in infants and young children; TB is a major contributor to under-5 mortality in TB-endemic settings. In the last few years, epidemiological and trial evidence in humans have supported the conclusion that BCG vaccination leads to several beneficial heterologous effects on all-cause mortality. BCG vaccination reduces all-cause mortality through beneficial nonspecific effects on the immune system; the importance of these effects has been formally recognized by the WHO. These "non-specific" beneficial effects suggest improved survival as the result of enhanced immune protection against nonrelated infections. Mechanisms for this heterologous effect are identified as immune alternative cross-reactivity and the recently described "immune training" effect of vaccination. This "training" targeted on the cells of the innate immune system could be related to epigenetic reprogramming of innate cells through a NOD2-related mechanism. Trained cells become more efficient at immune response against nonrelated pathogens after vaccination (see also ▶ Chap. 1).

In 2020 with the devastating COVID-19 pandemic causing nearly two million deaths, it has been *hypothesized that BCG vaccination could be a potential tool against COVID-19*. The question was whether BCG could offer protection against SARS-CoV-2 infection or reduce COVID-19 disease severity. Ecological studies have suggested that countries and regions that mandate BCG vaccination for the population have a lower number of infections and a reduced mortality from COVID-19, suggesting association between BCG vaccination policy and COVID-19 mortality. For Israeli adults aged 35 to 41 years, BCG vaccination in childhood

was associated with a similar rate of positive test results for SARS-CoV-2 compared with no vaccination, and the conclusion of the study did not support the idea that BCG vaccination in childhood has a protective effect against SARS-CoV-2 infection in adulthood. Because of the small number of severe cases, no conclusion about the association between BCG status and severity of disease could be reached. A history of BCG vaccination was associated with a decrease in the seroprevalence of anti–SARS-CoV-2 IgG and a lower number of health-care workers who self-reported experiencing COVID-19–related clinical symptoms (Escobar et al. 2020). Therefore, large randomized, prospective clinical trials of BCG vaccination are urgently needed to confirm whether BCG vaccination can confer a protective effect against COVID-19. Today we are waiting for the results of nearly 20 clinical trials that begun in 2020. These studies are being carried out in health-care personnel from different countries to find out if the BCG vaccine can protect against the COVID-19 disease (BRACE, CORONA studies), and in people over 60 years of age who are at greater risk of suffering the most serious forms of COVID-19 disease (Giamarellos-Bourboulis et al. 2020). A randomized clinical trial for enhanced trained immune responses through BCG vaccination to prevent infections of the elderly (ACTIVATE) is under way. Interim analysis of the results showed protection from new infections with major effect on the prevention of respiratory disease but larger randomized clinical trials to study the impact of BCG vaccination on morbidity and mortality associated with COVID-19 are needed.

17.8 Vaccination Schedules and Indications

The International Union Against Tuberculosis and Lung Disease (IUATLD) has suggested a number of criteria according to which it may be reasonable for a country to move from a policy of systematic vaccination with BCG to the selective vaccination of high-risk groups.

The IUATLD and WHO recommend suspension of systematic BCG only for the following criteria:

- There is an effective reporting system, and the average annual notification rate of smear-positive pulmonary TB is <5 per 100,000.
- The average annual notification rate of tuberculous meningitis is <1 per ten million inhabitants in the last 5 years.
- The average annual risk of TB infection is <0.1%.

The BCG vaccination is considered strictly necessary in the following cases:

- Newborn vaccination is recommended in countries with high incidence of TB.
- Children without PPD exposed to smear-positive patients with poor compliance or refusal of treatment, or when the treatment does not get the negative sputum (persistently smear-positive patients).
- Children without PPD who move to live in highly TB-endemic countries, especially where control programs and access to appropriate treatment is not possible and where the prevalence of multidrug-resistant TB is high.

17.8.1 Administration of BCG in HIV Patients

In countries with a high prevalence of TB and HIV, it is important to exercise caution when BCG is administrated routinely owing to the risk of disseminated BCG in HIV-infected infants (ranges of 400–1300 per 100,000 doses administered). Therefore, BCG vaccination is not appropriate for infants or adults with known HIV infection (or other immunodeficiency) or for those patients with a high degree of suspicion for HIV infection, even if unconfirmed by laboratory results.

The BCG vaccination should be administered to asymptomatic infants born to mothers with unknown HIV status in countries with a high TB prevalence. However, for asymptomatic infants with unknown HIV status born to mothers known to be infected with HIV

the optimal approach to BCG vaccination is uncertain. At present, the WHO recommends that routine childhood BCG immunization be continued until all elements of an HIV-testing program can be implemented.

In countries with a low incidence of TB, BCG immunization may be considered in children ≤5 years in the following circumstances:

- The child is continuously exposed to an untreated or ineffectively treated patient who has infectious pulmonary TB and neither separation from the infectious patient nor long-term primary preventive therapy is feasible.
- The child is continuously exposed to a patient who has infectious pulmonary TB caused by *M. tuberculosis* strains resistant to isoniazid and rifampin, and separation from the infectious patient is not feasible.
- Children moving to Europe from endemic countries.

17.8.2 Exposure to MDR-TB

The efficacy of BCG vaccination for persons who are travelling to endemic areas with expected exposure to drug-resistant TB is uncertain. However, given the potentially significant risk of MDR-TB treatment failure, together with the relatively low rate of complications related to BCG vaccination in immunocompetent individuals, some favor administering BCG vaccination to unvaccinated, tuberculin-negative individuals exposed to MDR-TB. Further studies are needed to reconcile the protective efficacy of BCG vaccination in the setting of multidrug-resistant TB exposure among older children and adults.

17.9 Administration with Other Vaccines or Products

The BCG vaccine can be administered concomitantly with other vaccines without increasing side effects. The immunogenicity obtained is similar to that obtained with separate administration. The main limitation is the need for administration in different anatomical sites.

Coadministration with any other vaccine is possible (including other live vaccines). BCG enhances T- and B-cell responses to unrelated vaccine antigens. Unexpectedly, BCG vaccination has affected responses to various vaccines differently whether administered at the time of priming, boosting, or even before priming. BCG enhances both Th1 and Th2 cytokine responses to unrelated antigens and extended its influence on antibody responses to oral polio vaccine (see ▶ Chap. 1).

Regional lymphadenitis cases have been reported after administering other vaccines in the same place in which BCG vaccination was applied. Therefore, it is not recommended to administer any other vaccine in the same limb within 3 months of BCG administration.

It is also recommended not to administer BCG vaccine if the patient has been treated with antibiotics during the previous 30 days.

17.10 Safety

Overall, the BCG vaccine is well tolerated. After 2–6 weeks of receiving the vaccine, a small papule appears that increases in size and changes into an ulcer. The lymphatic nodules in cervical and axillary areas may be temporarily enlarged.

After a period of about 3 months, a scar appears, which is permanent (◘ Fig. 17.5).

The safety of BCG vaccination has been widely proven because more than 4 billion units have been administered all over the world since 1921. The most common complication found with its use is the occurrence of regional lymphadenitis with or without suppuration (◘ Table 17.1). Other types of local reactions, such as abscess or ulcers, are rarely seen and are more related to the administration technique, which must be carried out under strictly aseptic conditions and always intradermally.

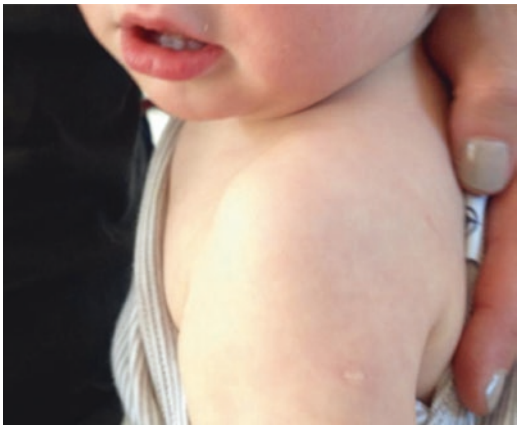


Fig. 17.5 Scarring after BCG vaccination. After 1–6 weeks, a small, red blister may appear where the injection was given. This should heal in a few weeks. After 6–12 weeks, the blister may turn into a small, weeping sore. The sore may take up to 3 months to heal, and leave a small scar. (Picture courtesy of Dr. Jesper Kjærgaard, Copenhagen University Hospital)

Table 17.1 Common local and systemic reactions to BCG (expressed as a percentage)

Systemic reactions	
Anorexia	<5%
Fever	<1%
Systemic reaction to vaccine	<0.003%
Asthenia	<5%
Osteitis	<0.0001%
Local	
Abscess	<0.01%
Lymphadenopathy	1–2%
Keloid	2–4%
Pain	95%
Erythema	95%
Ulceration	95% after 14 days
Pustule	95%
Swelling	95%
Pain	95%
Scar	95%

17.11 Warnings and Contraindications of the BCG Vaccine

General Warnings The BCG vaccine, when administered at birth, is highly reactogenic but safe. Swelling and scarring are common.

Anaphylactic reactions are seen only rarely, but their management should be prepared in advance and the patient should be closely observed for 15–30 min after administration.

The vaccine should be administered intradermally. Deeper administration could produce lymphadenitis or abscesses.

If an overdose of the vaccine is given, it may lead to suppurative lymphadenitis or, rarely, systemic infection.

Contraindications

- Immunocompromised patients, given that BCG vaccination is a live vaccine: congenital or acquired immunodeficiency due to immunosuppressive drugs such as corticosteroids, alkylating antineoplastic agents, radiation… Patients with HIV (with the exceptions as mentioned above).
- Patients with a positive PPD skin test or with TB.
- BCG should be avoided in pregnancy, especially in the first trimester, as it is a live vaccine.
- Hypersensitivity to the BCG vaccine or any of its components.
- Burns patients.
- Malnourished children.
- Active infection.
- Preterm infants with a birth weight less than 2.5 kg.
- Patients with blood diseases.
- Oncology patients.
- Patients who are already undergoing TB treatment.
- Patients with skin diseases. The area of insertion of the vaccine should be free of lesions.

17.12 Research on Alternative Routes of Administration of BCG

New routes of administration to the currently universally used intradermal route of BCG have been tested experimentally in nonhuman primates (NHP) trying to improve protection against the respiratory form of TB. The administration of BCG intravenously (IV) in macaque models shows a high protection against TB infection using 100 times the intradermal dose of BCG (Darrah et al. 2020). These preclinical results open the door to a better understanding of BCG protection, efficacy results demonstrate ability of IV BCG to substantially limit *M. tuberculosis* infection in a highly susceptible rhesus macaques model could have important implications in the preclinical evaluation of new candidates, as it could provide a prototype to identify biomarkers and immune mechanisms of protection induced by vaccines against TB. The enormous difficulty of using the IV route for mass vaccination campaigns and the potential safety risks of using 100 times the intradermal dose make its clinical use unlikely. The administration of BCG by respiratory route in the macaque model has shown great promise in conferring very good immunity and protection in NHP (Dijkman et al. 2019). If these results are confirmed in clinical studies, the aerosol route could be considered a possible universal vaccination route to BCG and new TB vaccine strategies. New studies of BCG administration by aerosol have been initiated recently (NCT03912207).

17.13 New Tuberculosis Vaccines in Clinical Trials

The most successful, licensed vaccines available today induce neutralizing antibodies that provide protective immunity. Animal and human studies of TB, however, suggest that a robust cellular immune response is required for protection against *M. tuberculosis* infection and disease. For this reason, most current clinical TB vaccine candidates are based on a variety of vectors, adjuvants, and antigens that induce classical TH1 cytokines such as IFN-γ or TNF-α from either CD4+ or CD8+ T cells.

TB vaccine development and the progress in clinical evaluation have been thoroughly reviewed recently (Sable et al. 2019) as well as the update on TB vaccine pipeline (Martin et al. 2020). Today, there are 14 different TB vaccines or TB vaccines strategies being studied in clinical trials (Fig. 17.6), and many more in preclinical development. Five of these trials are based on whole cell mycobacteria. The rest of them are various subunit-based approaches in which *M. tuberculosis* antigens are expressed as recombinant proteins

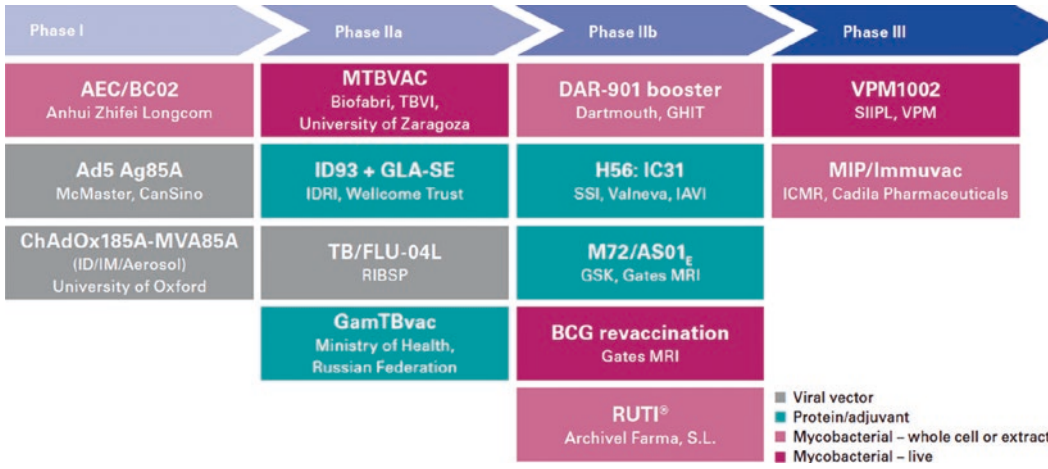


Fig. 17.6 The Global Clinical Development pipeline of TB vaccines in clinical trials. (WHO TB Report 2020)

that are either formulated with adjuvants or presented in recombinant viral vectors. BCG/BCG revaccination strategy showed a positive signal in prevention studies of *M. tuberculosis* infection and has been included for application in adolescents and adults vaccinated with BCG at birth.

WHO Preferred Product Characteristics for New TB vaccines focus on two strategic goals for developing safe, effective and affordable TB vaccines: (1) for adolescents and adults, and (2) for neonates and infants with improved safety and efficacy as compared to BCG. Given the central role that adolescents and adults with active pulmonary TB disease play in spreading *M. tuberculosis* infection, the prevention of pulmonary TB disease in adolescents and adults is the priority strategic target in TB vaccine development. While infants and young children with TB do not represent an important source of *M. tuberculosis* transmission, they represent an important, vulnerable group, and there is a need to improve upon the BCG vaccines currently in use. Considering a BCG replacement candidate nonspecific effects as in BCG will need to be considered.

The current global TB vaccine portfolio consists of three main types of vaccine strategies, which are either preventive or therapeutic. The preventive strategies embrace the priming BCG replacement vaccines and subunit BCG boosts (or enhancers). Therapeutic candidates that have reached clinical development to date comprise inactivated forms of mycobacteria being developed for patients with active TB. They receive TB drug therapy also in addition to this vaccine to shorten the duration of the therapy and to reduce the likelihood of recurrence after completion of treatment.

There are two main strategies for which research on prophylactic vaccines for TB prevention is focused:

- A better vaccine than the current BCG: more efficacious and longer lasting, or preventive of TB infection and disease in infants who have not been infected with *M. tuberculosis* (BCG replacement strategy).
- A BCG booster vaccine: for use as a heterologous boost in BCG-primed individuals, where BCG is given at birth and then boosting is applied with specific *M. tuberculosis* antigens. This strategy may be indicated in those patients who are latently infected, preventing infection and/or progression to active disease. Subunit vaccines are based on one or a few *M. tuberculosis*–specific protein antigens using viral vectors or adjuvants as the delivery system.

Replacement strategies for BCG are divided into two classes of live vaccines, namely recombinant BCG (rBCG) and live-attenuated *M. tuberculosis*. The rBCG candidates are designed to improve the efficacy of BCG by the insertion of other genes. Rationally attenuated *M. tuberculosis* of human origin is considered a classical Pasteurian approach to human vaccinology, expected to mimic natural infection without causing disease. Two BCG replacement vaccines are in the advanced stages of development: rBCG VPM1002 and MTBVAC. rBCG VPM1002 (rBCGΔUreC::hly) expresses listeriolysin (hly) from *Listeria monocytogenes* with deletion of the urease C (*ureC*) gene, MTBVAC is a live, rationally attenuated derivative of a human *M. tuberculosis* isolate, which belongs to lineage 4 (European–African–American), one of the most widespread lineages of *M. tuberculosis*. MTBVAC contains all the genes present in *M. tuberculosis* strains, including the genes that are deleted in *M. bovis* and RD1 region deleted in BCG. MTBVAC contains two independent stable deletion mutations in the virulence genes *phoP* and *fadD26.* These deletions were generated in the absence of antibiotic resistance markers, fulfilling the Geneva consensus requirements for progressing live mycobacterial vaccines to clinical trials. MTBVAC has completed two Phase I trials: the Phase Ia safety and immunogenicity results in adults conducted at the University of Lausanne and Phase Ib in Newborns in South Africa were satisfactory and immunological results encouraging. When given at the same dose as BCG (5×10^5 cfu), MTBVAC has shown a comparable safety pro-

file to BCG and more polyfunctional $CD4^+$ central memory T cells. The immunogenicity data show that MTBVAC is more immunogenic than BCG in newborns. MTBVAC is currently in clinical development, with the primary target population being newborns (BCG replacement vaccine) and the secondary target being adolescents and adults (BCG revaccination). Dose-defining Phase IIa trials in both target populations started in 2019 (► ClinicalTrials.gov NCT02933281) and in neonates (► ClinicalTrials.gov NCT03536117). Recently it was demonstrated that similarly to BCG, MTBVAC is able to induce trained immunity. Taken together, these data supported the efficacy clinical trials in high-burden countries where TB is endemic.

The first efficacy trial of a new TB vaccine after almost 100 years of use of BCG, was published in 2013. MVA85A vaccine is designed to increase immunity in children previously vaccinated with BCG and who are given the modified Ankara vaccine virus (MVA) to which the gene coding for the Ag85A major TB antigen had been introduced. The Phase IIb efficacy study consisted of a double-blind, placebo-control study in healthy children aged between 4 and 6 months, not infected with HIV and who had previously received BCG at birth, followed for more than 3 years. The result showed that 32 children (2%) of the 1399 vaccinated with BCG + MVA85A were diagnosed with TB and 39 children (3%) of the 1398 vaccinated with BCG + placebo. The difference between the two groups was not significant, and the interpretation of the result of the study was the absence of efficacy of MVA85A.

Two proofs of concept trials have been published with positive signals that encourage the preparation of Phase 2b efficacy studies with a greater number of volunteers for efficacy studies in endemic countries. BCG revaccination study in adolescents/adults studied the prevention of *M. tuberculosis* infection using interferon-γ release assays (IGRA) conversion QuantiFERON test in healthy South African adolescents This trial demonstrated that BCG/BCG revaccination reduced the rate of upper respiratory tract infections as compared to a subunit vaccine or placebo (2.1%, 9.4%, and 7.9%, respectively; $P < 0.001$ for both comparisons) suggesting that BCG revaccination could prevent respiratory diseases, including AMR forms of these diseases.

Another clinical trial that showed positive results in individuals previously infected with *M. tuberculosis* (LTBI) was with TB vaccine candidate M72/AS01E, which is a subunit candidate vaccine comprising two *M. tuberculosis* antigens (32A and 39A) formulated in the AS01E adjuvant for delivery. It was evaluated in a Phase IIb efficacy trial in in Kenya, South Africa, and Zambia among *M. tuberculosis*–infected, HIV-negative candidates. The data showed 54.0% protective efficacy in *M. tuberculosis*–infected young adult women, and the immunogenicity analysis after end of the 3-year follow-up showed that M72/AS01E elicited an immune response and provided protection against progression to pulmonary TB disease for at least 3 years. Although in LTBI individuals, this is the first time a proof-of-principle trial demonstrates vaccine-induced protection against clinical TB disease. However, whether M72/AS01 could provide protection against TB among *M. tuberculosis*–uninfected and HIV-negative individuals and in people from other geographical areas remain key questions to be answered. M72/AS01E has been exclusively licensed to the Medical Research Institute of Bill and Melinda Gates Foundation for further development.

At present, there are no accepted correlates of protection that, unto themselves, could support a decision to license a TB vaccine. Robust safety and immunogenicity data are needed for future efficacy trials of new TB vaccines. Therefore, the development of new vaccines against the pulmonary forms of TB are urgently needed for the control of TB.

Potential Conflicts of Interest CM is coinventor on a composition of matter patent "tuberculosis vaccine" at the University of Zaragoza. There are no other conflicts of interest.

Further Reading

Arbués, A., Aguilo, J. I., Gonzalo-Asensio et al. (2013). Construction, characterization and preclinical evaluation of MTBVAC, the first live-attenuated *M. tuberculosis*-based vaccine to enter clinical trials. *Vaccine* 31, 4867–4873.

Black GF, Weir RE, Floyd S, et al. BCG-induced increase in interferon-gamma response to mycobacterial antigens and efficacy of BCG vaccination in Malawi and the UK: two randomised controlled studies. Lancet. 2002;359:1393.

Blok BA, Arts RJ, van Crevel R, Benn CS, Netea MG. Trained innate immunity as underlying mechanism for the long-term, nonspecific effects of vaccines. J Leukoc Biol. 2015;98(3):347–56

Colditz GA, Brewer TF, Berkey CS, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. JAMA. 1994;271:698.

Darrah, P. A., Zeppa, et al. . (2020). Prevention of tuberculosis in macaques after intravenous BCG immunization. *Nature* 577, 95–102.

Dijkman, K., Sombroek, C. et al (2019). Prevention of tuberculosis infection and disease by local BCG in repeatedly exposed rhesus macaques. *Nature Medicine* 25, 255–262.

Escobar, L. E., Molina-Cruz, A. & Barillas-Mury, C. (2020). BCG vaccine protection from severe coronavirus disease 2019 (COVID-19). *Proc Natl Acad Sci USA* 117, 17720–17726.

Fine PE, Carneiro IA, Milstien JB, Clements CJ. Issues relating to the use of BCG in immunization programs: a discussion document. Geneva, Switzerland: Department of Vaccines and Biologicals, World Health Organization 1999. p.1. World Health Organization. 2011. The Immunological Basis for Immunization Series. Module 5: Tuberculosis.

Giamarellos-Bourboulis, E. J., Tsilika, et al. (2020). ACTIVATE: randomized clinical trial of BCG vaccination against infection in the elderly. *Cell* 1–49. Elsevier Inc.

Hamiel, U., Kozer, E. & Youngster, I. (2020). SARS-CoV-2 Rates in BCG-Vaccinated and Unvaccinated Young Adults. *JAMA* 323, 2340–2341.

Horvath CN, Shaler CR, Jeyanathan M, et al. Mechanisms of delayed anti-tuberculosis protection in the lung of parenteral BCG-vaccinated hosts: a critical role of airway luminal T cells. Mucosal Immunol. 2012;5:420.

Jensen KJ, Larsen N, Biering-Sørensen S et al. Heterologous immunological effects of early BCG vaccination in low-birth-weight infants in Guinea-Bissau: a randomized-controlled trial. J Infect Dis. 2015;211(6):956–67.

Kay AW, Blish CA, Delayed BCG. Vaccination – time to take a shot. J Infect Dis. 2015:211–5.

Kleinnijenhuis J, van Crevel R, Netea MG. Trained immunity: consequences for the heterologous effects of BCG vaccination. Trans R Soc Trop Med Hyg. 2015;109(1):29–35.

Mangtani P, Abubakar et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. Clin Infect Dis. 2014;58:470–80.

Marais BJ, Seddon JA, et al. Interrupted BCG vaccination is a major threat to global child health. Lancet Respir Med. 2016;4:251–3.

Martin, C., Aguilo, N., Marinova, D. & Gonzalo-Asensio, J. (2020). Update on TB vaccine pipeline. *Applied Sciences (Switzerland)* 10.

O'Neill, L. A. J. & Netea, M. G. (2020). BCG-induced trained immunity: can it offer protection against COVID-19? *Nature Reviews Immunology* 395, 497.

Ota MOC, Vekemans J, et al. Influence of *Mycobacterium bovis bacillus* Calmette-Guérin on antibody and cytokine responses to human neonatal vaccination. J Immunol. 2002;168:919–25.

Roy A, Eisenhut M, Harris RJ, et al. Effect of BCG vaccination against *Mycobacterium tuberculosis* infection in children: systematic review and meta-analysis. BMJ. 2014;349:g4643.

Sable, S. B., Posey, J. E. & Scriba, T. J. (2019). Tuberculosis Vaccine Development: Progress in Clinical Evaluation. *Clinical Microbiology Reviews* 33, 16076.

Schrager, L. K., Chandrasekaran, et al. (2018). WHO preferred product characteristics for new vaccines against tuberculosis. *The Lancet Infectious Diseases* 18, 828–829. Elsevier Ltd.

Soares AP, Kwong Chung CK, Choice T, et al. Longitudinal changes in CD4(+) T-cell memory responses induced by BCG vaccination of newborns. J Infect Dis. 2013;207:1084.

Spertini F, Audran R, Chakour R, et al. Safety of human immunisation with a live-attenuated Mycobacterium tuberculosis vaccine: a randomised, double-blind, controlled phase I trial. Lancet Respir Med. 2015;3:953–62.

Tait, D. R., Hatherill, M., et al. Final analysis of a trial of M72/AS01E vaccine to prevent tuberculosis. N Engl J Med. 2019;381:2429–39. https://doi.org/10.1056/NEJMoa1909953.

Tameris, M., Mearns, et al. (2019). Live-attenuated Mycobacterium tuberculosis vaccine MTBVAC versus BCG in adults and neonates: a randomised controlled, double-blind dose-escalation trial. *The Lancet Respiratory Medicine* 1–14.

Tarancón, R., Domínguez-Andrés, J et al (2020). New live attenuated tuberculosis vaccine MTBVAC induces trained immunity and confers protection against experimental lethal pneumonia. *PLoS Pathog* 16, e1008404.

Van Der Meeren, O., Hatherill, et al. . (2018). Phase 2b Controlled Trial of M72/AS01E Vaccine to Prevent Tuberculosis. *N Engl J Med* 379, 1621–1634.

Wilson ME, Fineberg HV, Colditz GA. Geographic latitude and the efficacy of bacillus Calmette-Guérin vaccine. Clin Infect Dis. 1995;20:982.

European Centre for Disease Prevention and Control/ WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2020–2018 data. Available at: https://www.ecdc.europa.eu/en/publications-data/tuberculosis-surveillance-and-monitoring-europe-2020-2018-data

WHO Global Tuberculosis Report 2020. Available at: https://www.who.int/publications/i/item/9789240013131

Pertussis Vaccines

Ulrich Heininger

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_18

18.1 Burden of Pertussis Disease

The clinical characteristics of pertussis disease are highly dependent on the host's basic immunity. Most if not all neonates and young infants (i.e., <3 months of age) of mothers who were not immunized against pertussis during pregnancy develop a cough when exposed to *Bordetella pertussis*, the causative agent of pertussis (or whooping cough). At this young age, infants are highly vulnerable for complicated disease, which includes apnea (in 49–58% of affected individuals), the need for supplemental oxygen (59–100%) and/or mechanical ventilation (27–100%), and pulmonary hypertension (11–39%). In accordance, most deaths due to *B. pertussis* infection occur in neonates and young infants with a case fatality rate of 1–3%.

Typical pertussis is a three-stage disease and usually occurs in unimmunized older infants and children, less frequently in adolescents or adults: after an incubation period of 7–10 days, the catarrhal phase begins with nonspecific nasal congestion, rhinorrhea, conjunctivitis, mild sore throat, and cough. Fever is uncommon. One to two weeks later, the paroxysmal stage follows. It is characterized by worsening coughs, cumulating in frequent paroxysmal spells, occurring day and night, with viscous secretions, vomiting, and the characteristic whoops terminating the coughing spell, but sometimes directly leading to the next one. Between these paroxysms, the patient appears well. After several weeks, the final convalescent stage of highly variable duration brings relief, with decreasing frequency and severity of coughing spells and accompanying symptoms.

Leukocytosis due to lymphocytosis is a hallmark of typical pertussis and the basis for most pulmonary complications, which may lead to respiratory failure with the need for exchange transfusion of extracorporeal membrane oxygenation.

In contrast, the clinical presentation of pertussis in immunized children and adolescents as well as in adults (even in those who are unimmunized), is frequently less typical, i.e., predominantly a nonspecific cough of variable duration. The cough frequently lasts for several weeks and because of the lack of characteristic signs such as paroxysms, vomiting, and whooping, it often remains undiagnosed unless it is linked to a case of typical pertussis or a knowledgeable physician considers pertussis in the differential diagnosis and applies appropriate diagnostic tests.

Complications are rare with atypical pertussis. In contrast, in patients with typical pertussis, severe coughing episodes, pneumothorax, rib fracture, herniated intervertebral disc, epistaxis, subconjunctival hemorrhage, subdural hematoma, hernia, rectal prolapse, urinary incontinence, and carotid artery dissection have been reported to be consequences of increased intrathoracic pressure.

Importantly, all patients with pertussis – typical or less typical – are contagious and therefore play an important role in transmission chains.

18.2 Pertussis Epidemiology

As has been shown in longitudinal seroprevalence studies (with anti-pertussis toxin IgG antibody values as a sensitive and the only specific marker of infection), most *B. pertussis* infections (affecting up to 20% of any population per year) remain asymptomatic. Fewer individuals, 0.5–1% (or 500–1000 per 100,000 of the population per year), develop a cough of ≥2 weeks' duration due to *B. pertussis* infection, and this is only detected in prospective studies. Among those, a variable fraction – depending on the basic immunity (see ▶ Sect. 18.1 above) – develop classic pertussis. In passive surveillance systems, the basis for nationwide mandatory reporting in many European countries, the yearly incidence of pertussis varies greatly, with values ranging from 0.01 to 96 per 100,000, where most countries report an incidence of approximately 10. These differences by all likelihood are not real, but these can be explained by the heterogeneity of surveillance systems in place and their associated case definitions. In the future, it is hoped that all European countries, or at least all European Union Member States will use the pertussis case definition proposed by the European Centre for Disease Prevention and Control (ECDC; ▶ Box 18.1).

Box 18.1 Pertussis Case Definition and Case Classification Proposed by the European Centre for Disease Prevention and Control (ECDC)

Pertussis *(Bordetella pertussis)*

Clinical criteria:

Any person with a cough lasting at least 2 weeks and at least one of the following three features:

- Paroxysms of coughing
- Inspiratory "whooping"
- Post-tussive vomiting

Or

Any person diagnosed as having pertussis by a physician

Or

Apneic episodes in infants

Laboratory criteria:

At least one of the following three:

- Isolation of *Bordetella pertussis* from a clinical specimen
- Detection of *Bordetella pertussis* nucleic acid in a clinical specimen
- *Bordetella pertussis*–specific antibody response

Serology results need to be interpreted according to the vaccination status

Epidemiological criteria:

- An epidemiological link due to human-to-human transmission

Additional information:

Incubation period 6–20 days, most often 10 days

Case classification:

A. Possible case
   - Any person meeting the clinical criteria
B. Probable case
   - Any person meeting the clinical criteria and with an epidemiological link
C. Confirmed case
   - Any person meeting the clinical and laboratory criteria

Note: The case definition and classification is that stipulated by the EU Commission Decision of 8 August 2012

18.3 Pertussis Vaccines

18.3.1 Whole-Cell Pertussis Vaccines

All whole-cell pertussis (wP) vaccines contain killed *B. pertussis* organisms of various genetic backgrounds. The first wP vaccines were developed shortly after *B. pertussis* was isolated, and the first results regarding protection were reported from the USA in 1925. After an animal model had been established ("Kendrick's mouse protection test") in 1947, standardization of vaccine production was possible and consecutive field studies in Great Britain were performed in the 1940s and 1950s. They demonstrated that the potency of wP vaccines as determined in the mouse protection test correlated with their clinical effectiveness in children. After that, wP, in combination with diphtheria and tetanus toxoids (DTP), was introduced into national immunization programs in many countries worldwide.

In the 1970s, concerns were raised based on serious adverse events (i.e., sudden infant death syndrome and various neurological illnesses including "encephalopathy" and epilepsy), which were reported following the use of DTP and were erroneously attributed to the wP component of the combination vaccine. It took decades to demonstrate that these events were coincidental rather than causally connected to DTP. Yet, these concerns, along with notable local side effects and fever induced by wP, led to the development of new pertussis vaccines. Such new acellular vaccines (see below) were first developed and then generally introduced for use in infants in Japan in 1981. Large field efficacy trials in Europe and Senegal, performed during the early 1990s, demonstrated better tolerability and acceptable efficacy of

aP vaccines (Tables 18.1 and 18.2) and have paved the way for the licensure of various aP combination vaccine products ever since.

In Europe, all countries except Poland and Serbia have switched from wP to aP vaccines for the primary immunization series in infants at some point in time between 1995 and 2010. There are two main disadvantages of wP vaccines compared with aP vaccines: higher reactogenicity, especially fever, and less standardized production, leading to highly variable lot-to-lot performance with regard to effectiveness (Tables 18.1 and 18.2). Yet, many countries outside Europe – especially low- and middle-income countries – still use wP vaccines in various combinations of diphtheria and tetanus toxoid (DTwP), with or without further components such as Hib, hepatitis B, and IPV.

18.3.2 Acellular Pertussis Vaccines

In the late 1970s, and throughout the 1980s and early 1990s, several vaccine manufacturers developed aP vaccines with the goal of better tolerability and similar efficacy compared with conventional wP vaccines. The former goal has clearly been reached (Table 18.1), but the latter unfortunately has not. Although aP vaccines (formulated as DTaP) performed better than one lot of DTwP vaccine produced in the USA when tested in efficacy trials in Italy and Sweden (Stockholm), overall efficacy estimates of DTwP vaccine were approximately 10% higher than those of DTaP after three or four doses in 3 + 0 (all doses in infants, no booster in the second year of life) and 3 + 1 (with a booster dose in the

Table 18.1 Comparative reactogenicity of whole-cell and acellular pertussis vaccines, by doses 1–3, as established in the United States Nationwide Multicenter Acellular Pertussis Trial

Adverse events	DTaP[a] (frequency in %)			DTP (frequency in %)		
	Dose 1 *n* = 1814	Dose 2 *n* = 1774	Dose 3 *n* = 1717	Dose 1 *n* = 370	Dose 2 *n* = 358	Dose 3 *n* = 342
Local						
Redness, any Redness, >2 cm	13.5 1.3	17.1 0.9	21.5 1.7	49.4 8.6	47.7 6.1	47.6 3.2
Swelling, any Swelling, >2 cm	8.7 1.7	12.1 1.4	13.3 2.2	39.7 16.5	34.1 9.5	35.7 5.6
Pain, moderate or severe Pain, severe	3.8 0.2	2.0 0.1	2.1 0.1	27.3 9.7	18.7 6.1	15.8 3.8
Systemic						
Fever (temperature ≥37.8 °C [100.1 °F])	4.2	11.3	15.8	27.3	34.1	37.7
Fever (temperature ≥38.4 °C [101.1 °F])	0.4	1.2	2.2	3.0	5.3	9.9
Fussiness, moderate or severe Fussiness, severe	6.6 2.0	7.7 1.6	6.7 1.3	20.6 3.8	23.5 7.0	17.3 4.7
Drowsiness	29.9	17.6	12.9	43.5	31.0	24.6
Anorexia	9.3	8.9	8.9	19.5	16.5	14.3
Vomiting	6.3	4.5	4.2	7.0	4.5	5.3
Use of antipyretic	39.3	36.7	36.3	60.5	59.8	61.4

Modified after Decker et al. (1995)
DTaP diphtheria–tetanus–acellular pertussis, *DTP* diphtheria–tetanus–pertussis
[a]Pooled data from 13 different DTaP products

Table 18.2 Comparative whole-cell and acellular pertussis vaccine efficacy as established in prospective randomized clinical trials

Country/ region	Study design	Schedule			
		Vaccine[a] efficacy	No. doses (age)	Typical pertussis (%)	Mild and typical pertussis (%)
Germany, Erlangen	Prospective cohort	aP-4	4 doses (3, 4, 6 + 15–18 months)	83	72
		wP	As above	93	83
Germany, Mainz	Household contact	aP-3	3 doses (3, 4, 5 months)	89	81
		wP	As above	98	Not reported
Germany, Munich	Case control	aP-2	4 doses (2, 4, 6, 15–25 months)	93	Not reported
		wP	As above	96	Not reported
Italy, Rome	Double-blind, prospective cohort	aP-3a	3 doses (2, 4, 6 months)	84	71
		aP-3b	As above	84	71
		wP	As above	36	23
Senegal	Household contact	aP-2	3 doses (2, 4, 6, 15–25 months)	74	Not reported
		wP	As above	92	Not reported
Sweden, Gothenburg	Double-blind, prospective cohort	aP-1	3 doses (3, 5, 12 months)	71	54
Sweden, Stockholm	Double-blind, prospective cohort	aP-2	3 doses (2, 4, 6 months)	59	42
		aP-3	As above	85	78
		wP	As above	48	41

wP whole-cell pertussis vaccine
[a]aP-1 = single component acellular pertussis vaccine, aP-2 = 2-component acellular pertussis vaccine, etc.

second year of life) immunization schedules, respectively (Table 18.2).

18.4 Safety and Reactogenicity

Tolerability of DTaP vaccines is good and not different from that of DT vaccines without the aP component. A detailed comparison of DTaP and DTwP reactogenicity profiles, as established in the United States Nationwide Multicenter Acellular Pertussis Trial, is shown in Table 18.1.

In the 1970s and 1980s, wP vaccines were held responsible for allegedly having caused "pertussis vaccine encephalopathy" in infants to the order of 1 per 330,000 doses within 7 days of immunization. However, careful investigations later demonstrated that what had been thought to be specific wP vaccine damage was in reality the result of various underlying morbidity with diverse etiopathogenesis, including genetic disorders such as the recently discovered SCN1A gene mutation, leading to Dravet syndrome. In other words, what was observed and reported was coincidence rather than cause and effect. Even before rare, specific underlying morbidities were discovered, it was epidemiologically shown that the increased risk of onset of cen-

tral nervous system disease potentially leading to brain damage within 7 days of immunization was offset by a decreased relative risk over the subsequent 3-week period such that the overall result was no increased risk for serious neurological disease with wP vaccines. However, despite such clear evidence against it, the myth of "pertussis vaccine damage" continues to prevail, especially on obscure internet fora.

Hypotonic–hyporesponsive episodes (HHEs) have been reported after many vaccines used in infants, with or without aP or wP components. However, the risk of HHEs is approximately tenfold higher with DTwP vaccine than with DTaP vaccine (approximately 1 per 15,000 vs. 1 per 1500 doses).

For children from the age of 4 years onward, adolescents, and adults without any upper age limit, acellular pertussis vaccines in combination with tetanus and diphtheria toxoids with reduced diphtheria and pertussis antigen content – therefore referred to as "Tdap" (tetanus–diphtheria–acellular pertussis) – have been licensed in Europe and elsewhere.

18.5 Real-World Effectiveness Data

Investigations into the real-world effectiveness of aP vaccines (and to a lesser extent, wP vaccines) are being conducted on an ongoing basis, with new evidence arising constantly. After the introduction of aP immunization programs in Europe in 1995 and onward, duration of protection after three or four doses was the focus of investigations. When it became apparent that efficacy waned with time after the last of three or four doses in infants and young children, booster doses were introduced in several countries in the early 2000s. Population-wide implementation of a fifth dose, usually at pre-school age and sometimes in adolescence, is more difficult to achieve than doses 4 and especially 1–3, and its low uptake contributes to the limited effectiveness. Moreover, it has recently become clear that even after five doses protection against pertussis does not last very long: In a matched case–control study from Washington State, USA, adolescents and young adults (11–19 years of age) with suspected, probable, and confirmed pertussis were identified, and vaccine effectiveness was calculated based on pertussis immunization history. Among those individuals who had received only acellular pertussis vaccines, Tdap vaccine effectiveness was 73% at 1 year and 34% at 2–4 years following their last pertussis vaccine dose. Similarly, waning immunity was shown in a study in Wisconsin, where a pertussis outbreak had occurred in 2012. Tdap effectiveness in preventing laboratory-confirmed pertussis decreased with increasing time since receipt of the last Tdap vaccine, with values of 75%, 68%, 34%, and 12% among those who received their last Tdap dose in 2012, 2011, 2010, and 2009/2008, respectively. Therefore, the introduction of further booster doses in adolescents, and even adults, was the next step that some but by far not all countries in Europe have taken in recent years. However, with aP vaccines of suboptimal effectiveness, control of pertussis is challenging if not impossible. Recently, this has raised discussions about the re-introduction of wP, for example, as part of sequential wP/aP immunization schedules. Although some wP vaccines do appear to be more efficacious than any aP vaccine, there is lot-to-lot inconsistency with poor efficacy (<50%) for some wP products (◘ Table 18.2). As, unfortunately, there is a lack of a reliable serological correlate of vaccine protection and no reliable animal models that would allow wP vaccine performance to be predicted, their use in the field is a constant lot-to-lot lottery.

18.6 Pertussis Vaccine Recommendations

Currently, so-called "2 + 1" and "3 + 1" DTaP immunization schedules are used in 16 (previous edition of this textbook, 2017: 8!) and 15 (2017: 23) European countries, respectively, organized under the umbrella of the ECDC (◘ Fig. 18.1). The first figure stands for the number of priming doses in infants (i.e., 2

Fig. 18.1 Recommended pertussis immunization schedules in Europe (as of October 4, 2020, corrected for Germany which has introduced the 2 + 1 schedule in June 2020)

or 3) and the "+1" stands for the reinforcing last dose of the primary series, usually given around the first birthday. The apparent heterogeneity in time points reflects variable interpretations of data by national immunization technical advisory groups to the governments, variable histories of the development of such recommendations, and associations with scheduled health care visits such as the "well baby visits," which again may vary from country to country.

In addition to regularly scheduled doses throughout childhood, some countries do recommend pertussis immunization in specific situations, with the goal of decreasing the risk of transmission to young, vulnerable infants ("cocooning"). Unfortunately, several studies, including one from Switzerland, have shown that cocooning is extremely challenging from a logistic point of view and a complete "cocoon" around the newborn or young infant is hardly ever achieved, especially in large households.

Today, among various strategies of maternal and paternal immunization, the concept of immunization in pregnancy is most promising. The ideal timing is during the second or early third trimester to guarantee optimal amounts of maternal anti-PT-IgG antibodies transferred via the placenta to the unborn fetus. Maternal and paternal immunization means that women's and men's pertussis immunization status is brought up to date as part of family planning before the woman's pregnancy or catching up with pertussis immunizations after delivery, if they were missed before. Basically, this leads to cocooning of the young infant, as discussed above. In addition to this, immunizing a woman *during* pregnancy brings a new dimension of protection to the infant, i.e., *direct protection* via transplacental transfer of high quantities of maternal anti-pertussis toxin (PT) IgG antibodies. A case–control study, performed as part of a national vaccination program for pregnant women in the UK between October 2012 and July 2013, demonstrated that only 17% of mothers of infants (<8 weeks of age) with pertussis compared to 71% of mothers of healthy age-matched controls had been immunized against pertussis in pregnancy. This resulted in a protective effectiveness of immunization in pregnancy of 93%. It was further shown in Belgium that the average PT antibody levels in children whose mothers had been vaccinated against pertussis during pregnancy were much higher than those in children of unvaccinated mothers (101 vs. 12 IU/ml and 16 vs. 1 IU/ml at birth, and at the age of 2 months, respectively). When measured again 4 weeks after completion of the primary immunization 3 dose series at age 2, −3, and −4 months of age, however, anti-PT values in infants of vaccinated mothers were lower than those in control children (29 vs. 54 IU/ml), and this difference was still present after the fourth dose at 15 months of age (36 vs. 57 IU/ml).

The clinical significance of this blunting of the child's immune response to aP vaccine is unclear because of the lack of a reliable serological correlate of immunity and must be further evaluated in prospective epidemiological studies. One such study performed in the UK has provided convincing evidence of protection against pertussis provided by immunization in pregnancy beyond the infant's own first two doses of acellular pertussis containing combination vaccines. This additional protection from immunization of the infant's mother during pregnancy, as may be expected, is no longer evident after the third infant dose.

Given the benefit of significant protection during the first months of life in infants, these observations do not question pertussis immunization in pregnancy. So far, no safety concerns have arisen with regard to pertussis immunization in pregnant women. In an observational study based on the US Vaccine Safety Datalink, which accompanied the introduction of the immunization program in pregnant women in 2012 in the USA, no safety signals were detected. Today, in addition to England and Wales and the USA, an increasing number of countries recommend pertussis (Tdap) immunization for pregnant women.

However, given the suboptimal protective power of currently available aP vaccines, the search for "better" vaccines is ongoing.

Intensive efforts are underway to identify biomarkers that would predict protection from *B. pertussis* infection and/or disease and would then promote the development of new vaccines, which would elicit a protective immune response against *B. pertussis*. Although we may dream about a new generation of such better performing pertussis vaccines, the best use of aP (and wP, where still in use) vaccines should be made. This includes the optimization of vaccine coverage in the whole population and the timely administration of the recommended doses in infants and young children.

Further Reading

Acosta AM, DeBolt C, Tasslimi A, Lewis M, Stewart LK, Misegades LK, Messonnier NE, Clark TA, Martin SW, Patel M. Tdap vaccine effectiveness in adolescents during the 2012 Washington State pertussis epidemic. Pediatrics 2015;135:981–9.

Amirthalingam G, Campbell H, Ribeiro S, Fry NK, Ramsay M, Miller E, Andrews N. Sustained effectiveness of the maternal pertussis immunization program in England 3 years following introduction. Clin Infect Dis 2016;63(Suppl 4):S236−S43.

Berkovic SF, Harkin L, McMahon JM, Pelekanos JT, Zuberi SM, Wirrell EC, Gill DS, Iona X, Mulley JC, Scheffer IE. De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study. Lancet Neurol 2006;5:488–92.

Büttcher M, Heininger U, Braun M, Bonhoeffer J, Halperin S, Heijbel H, de Menezes MR, Vermeer-de Bondt P, The Brighton Collaboration HHE Working Group. Hypotonic-hyporesponsive episode (HHE) as an adverse event following immunization in early childhood: case definition and guidelines for data collection, analysis, and presentation. Vaccine 2007;25:5875–81.

Cherry JD. Epidemic pertussis and acellular pertussis vaccine failure in the 21st century. Pediatrics 2015;135:1130–2.

Cherry JD, Heininger U. Pertussis and other *Bordetella* infections. In: Feigin RD, Cherry JD, Demmler-Harrison GJ, Kaplan SL, editors. Textbook of pediatric infectious diseases. 6th ed. Philadelphia: Saunders; 2009. p. 1683–706.

Dabrera G, Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Fry NK, Ramsay M. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012–2013. Clin Infect Dis 2015;60:333–7.

Decker MD, Edwards KM, Steinhoff MC, Rennels MB, Pichichero ME, Englund JA, Anderson EL, Deloria MA, Reed GF. Comparison of 13 acellular pertussis vaccines: adverse reactions. Pediatrics 1995;96:557–66.

European Centre for Disease Prevention and Control (ECDC). Pertussis. Stockholm: ECDC. n.d. Available from: http://ecdc.europa.eu/en/activities/surveillance/euvac/case_definition/Pages/pertusis.aspx.

Forsyth KD, Campins-Marti M, Caro J, Cherry JD, Greenberg D, Guiso N, Heininger U, Schellekens J, Tan T, von König CH, Plotkin S, Global Pertussis Initiative. New pertussis vaccination strategies beyond infancy: recommendations by the Global Pertussis Initiative. Clin Infect Dis 2004;39:1802–9.

Heininger U, Cherry JD. Pertussis immunisation in adolescents and adults – Bordetella pertussis epidemiology should guide vaccination recommendations. Expert Opin Biol Ther 2006;6:685–97.

Heininger U, André P, Chlibek R, Kristufkova Z, Kutsar K, Mangarov A, Mészner Z, Nitsch-Osuch A, Petrović V, Prymula R, Usonis V, Zavadska D. Comparative epidemiologic characteristics of pertussis in 10 central and Eastern European Countries, 2000–2013. PLoS One 2016;11(6):e0155949.

Kharbanda EO, Vazquez-Benitez G, Lipkind HS, Klein NP, Cheetham TC, Naleway AL, Lee GM, Hambidge S, Jackson ML, Omer SB, McCarthy N, Nordin JD. Maternal Tdap vaccination: coverage and acute safety outcomes in the vaccine safety datalink, 2007–2013. Vaccine 2016;34:968–73.

Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. N Engl J Med 2012;367:1012–9.

Koepke R, Eickhoff JC, Ayele RA, Petit AB, Schauer SL, Hopfensperger DJ, Conway JH, Davis JP. Estimating the effectiveness of tetanus-diphtheria-acellular pertussis vaccine (Tdap) for preventing pertussis: evidence of rapidly waning immunity and difference in effectiveness by Tdap brand. J Infect Dis 2014;210:942–53.

Maertens K, Caboré RN, Huygen K, Hens N, Van Damme P, Leuridan E. Pertussis vaccination during pregnancy in Belgium: results of a prospective controlled cohort study. Vaccine 2016;34:142–50.

McGirr A, Fisman DN. Duration of pertussis immunity after DTaP immunization: a meta-analysis. Pediatrics 2015;135:331–43.

Nieves D, Heininger U, Cherry J. *Bordetella pertussis* and other *Bordetella* spp. infections. In: Wilson CB, Nizet V, Maldonado YA, Remington JS, Klein JO, editors. Remington and Klein's infectious dis-

eases of the fetus and newborn infant. 8th ed. Philadelphia: Elsevier Saunders; 2016. p. 598–616.

Urwyler P, Heininger U. Protecting newborns from pertussis – the challenge of complete cocooning. BMC Infect Dis 2014;14(1):397. https://doi.org/10.1186/1471-2334-14-397.

Vygen-Bonnet S, Hellenbrand W, Garbe E, von Kries R, Bogdan C, Heininger U, Röbl-Mathieu M, Harder T. Safety and effectiveness of acellular pertussis vaccination during pregnancy: a systematic review. BMC Infect Dis 2020;20(1):136. https://doi.org/10.1186/s12879-020-4824-3.

Winter K, Cherry JD, Harriman K. Effectiveness of prenatal Tdap vaccination on pertussis severity in infants. Clin Infect Dis 2017a;64(1):9–14.

Winter K, Nickell S, Powell M, Harriman K. Effectiveness of prenatal versus postpartum Tdap vaccination in preventing infant pertussis. Clin Infect Dis 2017b;64(1):3–8.

Haemophilus influenzae Type b (Hib) Vaccines

Mary P. E. Slack

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_19

19.1 Introduction

Haemophilus influenzae is a human-restricted pathogen that colonizes the nose and throat, and to a lesser extent the conjunctivae and genital tract. *H. influenzae* was first identified as a pathogen by Koch in 1883, who described small gram-negative bacilli in conjunctivitis. In 1889–1892 a major outbreak of influenza swept across Europe. Pfeiffer examined sputum from patients suffering from influenza and reported "in every case … a similar type of bacillus was found in absolutely pure culture … and in almost incredible numbers." He had difficulty in growing the bacillus until he added blood to the culture medium.

Continued belief that *Bacillus influenzae* (or Pfeiffer's bacillus) was the cause of influenza resulted in it being specifically named *Haemophilus influenzae*. In 1922, Kristensen proposed that this organism was a secondary invader and not the primary cause of influenza. In 1933, Smith, Andrewes and Laidlaw established that influenza was a viral infection, but the name of the bacterium has remained unchanged.

In 1933, Margaret Pittman differentiated *H. influenzae* into two major groups: encapsulated and non-capsulated strains (more commonly described as non-typeable *Haemophilus influenzae*: NTHi). She also described the six antigenically and chemically distinct types of capsulated strains; designated Pittman types a to f and identified type b (Hib) as of predominant importance in causing meningitis and other systemic haemophilus infections. The most virulent serotype is Hib.

In 1933, Fothergill and Wright showed that blood of young children, aged less than 2 years, had absent or low levels of bactericidal activity against the *H. influenzae* type b polysaccharide capsule, whereas blood from older children and adults did demonstrate bactericidal activity against Hib. They also noted that most cases of Hib meningitis occurred in young children, leading them to speculate that naturally acquired antibodies to the polysaccharide capsule were protective against serious Hib infections. The rarity of infections in the first 2 months of life correlates with the presence of maternal antibodies to Hib and the occurrence of infection in early infancy with the absence of antibodies having such specificity. As the mean level of Hib antibodies in the population rises, so Hib infections decline (Fig. 19.1).

19.2 Burden of Disease

Before the introduction of Hib conjugate vaccine, Hib was the most common cause of bacterial meningitis in children, 75% of whom were over 2 months and under 3 years

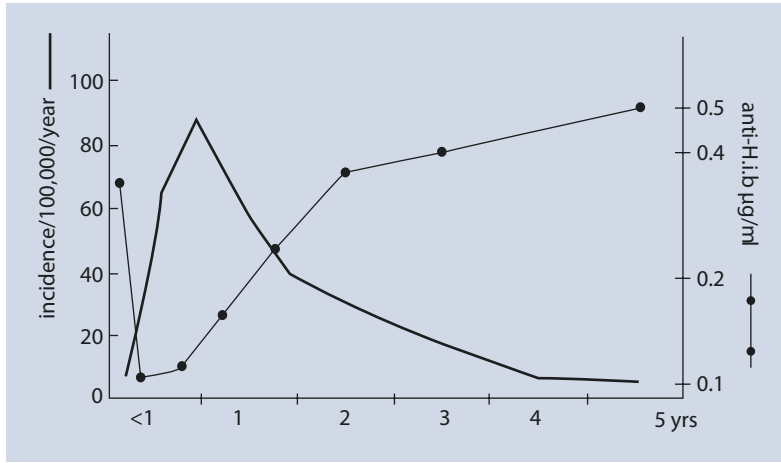


Fig. 19.1 Incidence of *H. influenzae* meningitis (heavy solid line) during the first 5 years of life and the corresponding mean level of anti-polyribosyl ribitol phosphate (PRP) (Hib) antibodies (thin line) (Peltola et al. 1977)

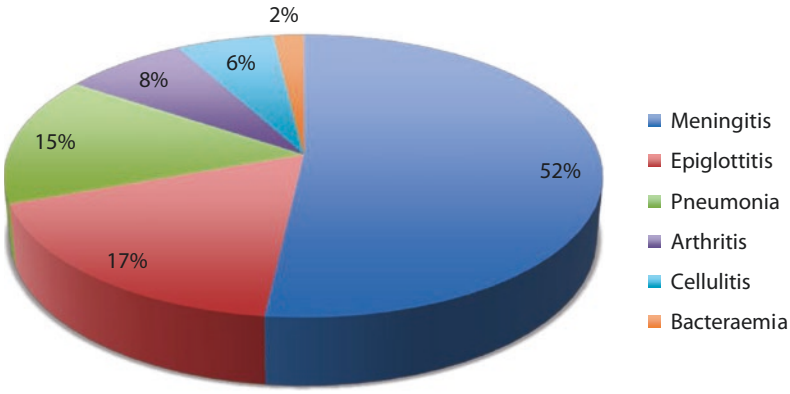


Fig. 19.2 Spectrum of invasive infections caused by Hib in the UK. Prospective surveillance data in all ages for 2 years before the introduction of routine Hib immunization (Anderson et al. 1995)

of age. Hib meningitis had a case fatality ratio of 5–10%, with up to one-third of survivors suffering significant sequelae, including deafness, intellectual impairment, cerebral palsy and epilepsy. Hib was also the most common cause of acute epiglottitis in children, which generally occurred in children aged between 2 and 4 years of age. Other manifestations of invasive Hib infection include bacteraemia, periorbital cellulitis, septic arthritis, osteomyelitis and pneumonia (Fig. 19.2).

The mean annual incidence per 100,000 children aged <5 years of invasive Hib disease prior to the introduction of Hib conjugate vaccine in Europe was 23/100,000, with higher incidences seen in northern Europe (Fig. 19.3) than in southern European countries. In some parts of the world and some populations, much higher rates were reported, ranging from 60–130/100,000 children <5 years in the USA to 450/100,000 in Indigenous populations in Australia, Canada and the USA.

19.3 Pathogenesis

H. influenzae is transmitted by aerosols of respiratory secretions or by direct contact with contaminated material. The primary event is colonization of the nasopharynx. Before the introduction of Hib vaccines, 3–5% of healthy pre-school children in industrialized countries were asymptomatic Hib carriers. The rate of non-typeable *H. influenzae* carriage is much higher. Asymptomatic Hib carriage can persist for up to 6 months.

Prior infection with respiratory viruses, such as influenza, predisposes to nasopharyngeal carriage by several mechanisms, including obstruction to the outflow of respiratory secretions, depression of local immunity and suppression of mucociliary clearance. The rate of Hib carriage varies with age, crowding, geography and vaccine coverage in a population.

Invasive Hib disease follows invasion of the bloodstream. Recent viral infection is a risk factor for developing invasive Hib disease, by facilitating the attachment of Hib to the respiratory epithelium. The risk of invasive Hib disease is increased in children with certain comorbidities, including sickle cell disease, asplenia, malignancies and antibody deficiency syndromes.

The capsule of Hib is composed of polyribosylribitol phosphate (PRP). PRP is the single most important major virulence determinant for invasion of the blood stream because it resists phagocytosis, complement-mediated bacteriolysis and splenic clearance. Studies on unimmunized individuals in Finland indicated that serum anti-PRP antibodies of ≥0.15 μg/mL correlated with a decreased incidence of Hib meningitis. Further studies established that a concentration of ≥0.15 μg/mL provides short-term protection against invasive Hib disease, but

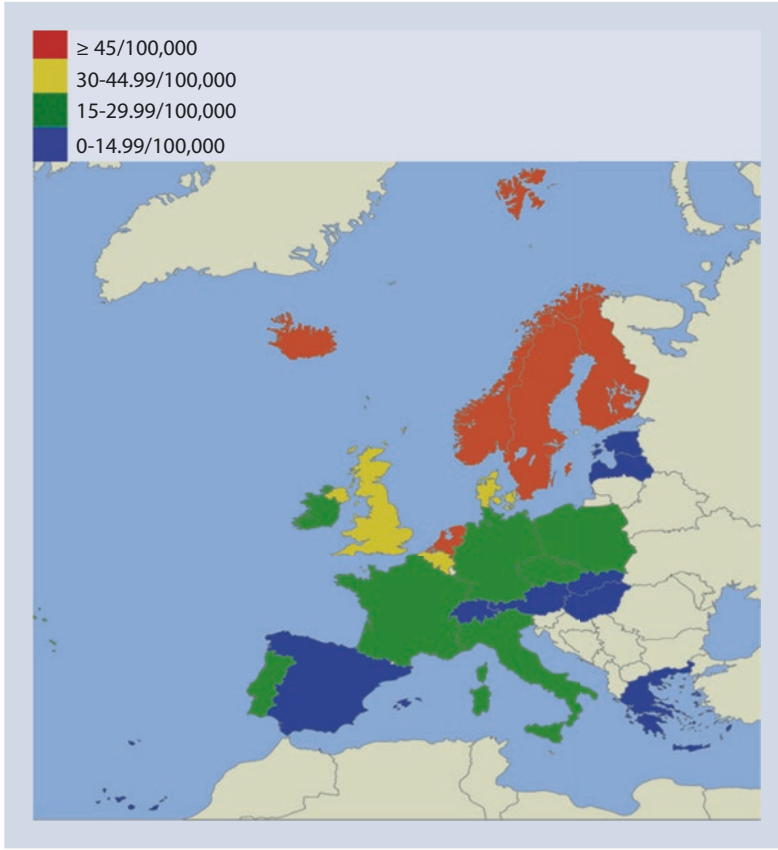


Fig. 19.3 Annual incidence of invasive Hib disease/100,000 <5 years in Europe before the introduction of routine Hib immunization (data from EU-IBIS reports)

long-term protection requires a concentration of ≥1.0 μg/mL.

19.4 Hib Polysaccharide Vaccine

The first Hib vaccine was a PRP plain polysaccharide vaccine, which was used in a field trial in Finland. This trial involving 100,000 children aged 3 months to 5 years demonstrated an age-dependent response to PRP. PRP polysaccharide vaccine had no demonstrable effect on nasopharyngeal carriage of Hib and thus did not interrupt transmission of Hib or produce herd protection. Polysaccharide vaccines activate B cells via a T-helper cell–independent pathway, which is poorly developed in children aged <18 months and characterized by lack of immune memory, short-lived antibody responses and poor immunogenicity.

19.5 Hib Conjugate Vaccines

In the late 1980s, conjugate Hib vaccines were developed which increased the immunogenicity of PRP polysaccharide. The polysaccharide–protein conjugate induced a T-cell-dependent response. T-cell-dependent responses develop much earlier in infants than T-cell-independent responses and infants can respond to polysaccharide–protein conjugate vaccines from the age of 6 weeks.

Protein antigens encourage class switching from IgM to IgG via T-helper cells. The IgG is predominantly IgG1 subclass, which in vitro induces complement-mediated opsonic activity and bacteriolysis. In addition, immunizing with a conjugate vaccine results in antibodies with higher avidity compared to those produced after immunization with plain PRP polysaccharide, with the added benefit of avidity maturation.

Protein–polysaccharide conjugate vaccines also have a marked impact on nasopharyngeal carriage. By reducing nasopharyngeal carriage of Hib, transmission to other susceptible unimmunized children and adults is interrupted, reducing infection in other age groups. This effect is known as herd protection.

Four different Hib vaccines were initially developed. They differed in the protein carrier used, the length of the PRP saccharide and the method of protein–polysaccharide conjugation. The four protein carriers were tetanus toxoid (PRP-TT), diphtheria toxoid (PRP-D), *Neisseria meningitidis* outer membrane protein complex (PRP-OMP) and a non-toxic mutant *Corynebacterium diphtheriae* protein CRM 197 (PRP-CRM).

Although the different Hib vaccines were equally immunogenic in adults, they elicited differing immune responses in children aged <2 years. The PRP-D conjugate was the least immunogenic in infants, eliciting an anti-PRP antibody titre ≥1.0 μg/mL in ≈30% of infants after two or three doses, and was subsequently withdrawn.

The other three vaccines are highly immunogenic in children aged >18 months. Their immunogenicity varies in children aged <18 months. PRP-OMP vaccine stimulates the highest antibody concentration with a single dose administered at 2 months of age eliciting antibody titres ≥1.0 μg/mL in 70–80% of infants. PRP-OMP was the preferred vaccine for use in populations where there was a high burden of disease in very young infants, for example, Indigenous Australian, American Indian and Alaska Native infants. PRP-TT and PRP-CRM have similar immunogenicity and there is no significant difference in the percentage of infants achieving anti-PRP antibody titres of ≥1.0 μg/mL after three priming doses. A booster dose of any of the PRP vaccines administered in the second year of life results in seroprotective levels of anti-PRP antibodies, irrespective of the PRP-vaccine used for the primary immunization series.

19.6 Combination Vaccines

Following the successful introduction of monovalent Hib conjugate vaccines, the Hib component was incorporated into combination vaccines (see ▶ Chap. 20). However, the combination may result in a significantly reduced anti-PRP antibody response compared to that achieved by a separate Hib conjugate vaccine. The Hib component has been combined with diphtheria toxoid (D), tetanus toxoid (T), whole-cell Pertussis (wP), acellular Pertussis (aP), inactivated polio (IPV) and Hepatitis B (HepB) as a component of pentavalent and hexavalent vaccines. It has also been combined with Meningococcal group C – tetanus toxoid (MenC-TT) as a dual vaccine Hib-MenC-TT and with Meningococcal groups C and Y as a trivalent vaccine (MenCY-TT) (Table 19.1).

Table 19.1 Some examples of Hib-containing vaccines available in Europe in 2021

Name	Characteristics	Manufacturer	Type
Act-Hib	Hib (PRP-TT)	Sanofi Pasteur	Monovalent
Hiberix	Hib (PRP-TT)	GSK	Monovalent
Hexacima/ Hexyon/Hexaxim	DTaP–HepB–IPV–Hib (PRP-TT)	Sanofi Pasteur	Hexavalent
Infanrix hexa	DTaP–HepB–IPV–Hib (PRP-TT)	GSK	Hexavalent
Vaxelis	DTaP–HepB–IPV–Hib (PRP-TT)	MCM	Hexavalent
Infanrix-IPV-Hib	DTaP–IPV–Hib (PRP-TT)	GSK	Pentavalent
Pentavac	DTaP–IPV–Hib (PRP-TT)	Sanofi Pasteur	Pentavalent
Menitorix	MenC–Hib (PRP-TT)	GSK	Bivalent
MenHibrix	MenCY-Hib (PRP-TT)	GSK	Trivalent

19.7 Introduction of Hib Conjugate Vaccines in Europe

Hib conjugate vaccine was included in the National Immunization Programme (NIP) of Finland in 1986, and over the next 20 years was added to the NIP schedule in all European countries.

19.8 Impact of Hib Conjugate Vaccines

Following the introduction of routine Hib conjugate vaccination in many European countries, an international collaboration was established in 1996 to monitor the impact of Hib conjugate vaccine on the epidemiology of invasive *H. influenzae* disease. Data on invasive *H. influenzae* disease was collected from 25 European countries between 1999 and 2006 by the European Union Invasive Bacterial Infections Surveillance Network (funded by the European Commission DG SANCO). In 2007, the surveillance activities were transferred to the European Centre for Disease Prevention and Control (ECDC). Between 2007 and 2014, 12 European countries reported 10,624 cases of invasive *H. influenzae* infection to ECDC. The majority of isolates were non-typeable *H. influenzae* (NTHi) (78%), 9% were Hib, 9% were *H. influenzae* serotype f (Hif) and 3% were serotype e (Hie). By 2014, the incidence of invasive Hib infection across Europe had declined to 0.65/100,000 in children aged <1 year and 0.18/100,000 in children aged 1–4 years. Invasive NTHi infections occur predominantly in neonates and older adults, the majority of whom have underlying comorbidities. Invasive Hif and Hie infections also mainly occur in older adults with underlying risk factors.

Hib conjugate vaccine is now included in the NIP of all European countries. The schedules of vaccine administration vary, with some countries giving three doses in the first year, followed by a booster in the second year of life, and others giving two doses in infancy plus a booster dose after the first birthday (Fig. 19.4). In 2013, France changed the schedule from 3 + 1 to 2 + 1 doses (2, 4 and 11 months).

Multiple Hib containing vaccines have been used in Europe. Countries have changed the Hib vaccine used over time but overall there has been a convergence towards the use of pentavalent or hexavalent combination vaccines (Fig. 19.4).

19.9 Safety of Hib Conjugate Vaccines

All the Hib conjugate vaccines have an excellent safety profile. Mild local reactions, including redness, induration, and swelling are reported to be more common with PRP-TT than with PRP-CRM or PRP-OMP.

19.10 Hib Vaccine Failures

Although Hib conjugate vaccines are highly effective, vaccine failures do occasionally occur. Clinical and immunological evaluation is recommended for children who develop invasive Hib disease despite a full course of Hib vaccinations.

19.11 UK Hib Vaccine Experience: Lessons Learned

Routine Hib immunization was introduced in the UK in October 1992. Three doses of Hib conjugate vaccine (PRP-TT; Pasteur Merieux) given at 2, 3 and 4 months of age were offered to all infants <1 year old. There was no booster dose in the second year of life. It was believed that a booster dose would not be needed as immunological memory was expected to provide long-term protection. A catch-up programme of a single dose of PRP-CRM vaccine was offered to children aged 1–4 years over the first year of the national infant immunization programme.

Following the introduction of Hib conjugate vaccination in the UK, there was a rapid and sustained decline in invasive Hib disease (Fig. 19.5) with the annual attack rate

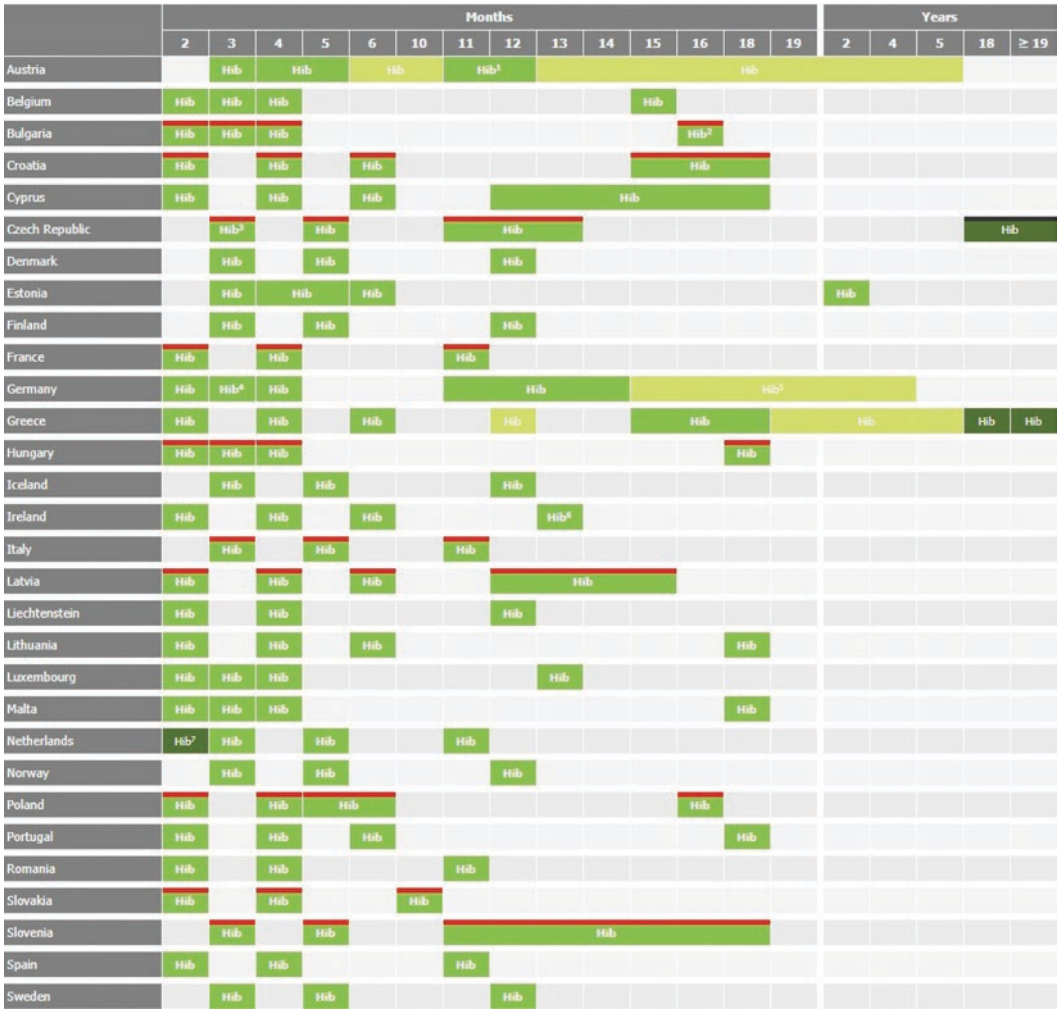


Fig. 19.4 Recommended Hib immunization schedules for European countries: 2021. (Reproduced with permission from: ► https://www.ecdc.europa.eu/en/publications-data/ecdc-vaccine-scheduler)

Footnotes:

(1) Minimum interval of 6 month after second dose

(2) Not earlier than 12 months after the third dose

(3) The first dose of hexavalent vaccine is given from the end of the second month of life, at intervals of 2 months between the first and the second dose, and the third dose given between the eleventh and thirteenth months of the child's age

(4) Optional doses if monovalent and other combination vaccines are used

(5) Number of doses necessary varies according to age

(6) Hib/MenC combined vaccine

(7) Recommended only in specific circumstances, for example: infants born to a mother not vaccinated against pertussis during pregnancy or infants born to a mother infected with Hepatitis B

The contents of this report are covered by the ECDC legal notice. See: ► https://ecdc.europa.eu/en/legal-notice. The report reflects the state of submissions in the ECDC vaccination schedule platform as of 2021-06-22 at 13:22. Red line above: mandatory vaccination, Blue line above: vaccination not covered by national Health System

General recommendation

Recommendation for specific groups only

Catch-up (e.g. if previous doses missed)

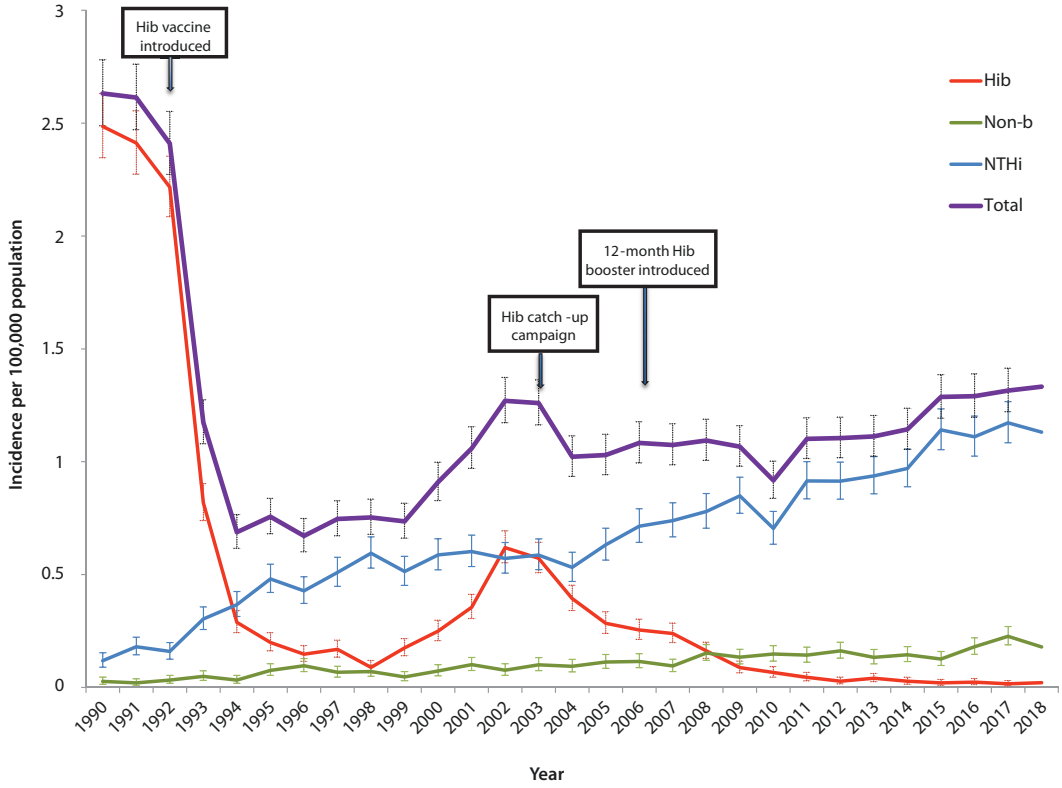


Fig. 19.5 Incidence of invasive *H. influenzae* disease in England by serotype: 1990–2018 (data from Public Health England)

for invasive Hib disease in children <5 years falling from 23.8/100,000 in 1991–1992 to 1.8/100,000 in 1993–1994. The decline in vaccinated age groups was soon followed by a decline in other age groups through indirect (herd) protection. By 1998 the incidence of invasive Hib disease in children aged <5 years had fallen to 0.63/100,000. There were estimated to be 2.2 vaccine failures/100,000 vaccinated children (95% CI, 1.8–2.7). Vaccine failures were uncommon. Although the vaccine effectiveness waned with time it remained high (>95%) until the sixth year of life.

From 1999, there was a resurgence in cases of Hib infection in children (Fig. 19.5) with 134 cases in <5 years in 2002 versus 31 cases in 1996. There appear to be several reasons for this resurgence. The vaccine effectiveness among children immunized in infancy was lower than had been anticipated. Among children <5 years who developed invasive Hib infection between 1993 and 2000, the vaccine effectiveness (VE) was estimated to be 57% (95% CI, 43–67). The VE was lower in children immunized in infancy compared to those who received a single dose of Hib vaccine as part of the catch-up programme and the VE in those immunized in infancy declined significantly over time ($p = 0.004$), declining to zero after 1 year. This lower VE only became apparent when the direct and indirect protection provided by the catch-up campaign in children aged 1–4 years began to wane. By 1998, all children aged <5 years had only received routine infant immunization in early infancy.

A further reason for the resurgence was a shortage of the DTwP-Hib vaccine that was being used in the UK, which led to approximately half of infants receiving an alternative combination vaccine containing acellular pertussis component. DTaP-Hib vaccines have been shown to have lower Hib immunogenicity, especially when used in an early accelerated infant schedule, as was the case in the UK. There is evidence that combination DTaP-Hib vaccines can elicit a significant

reduction in the anti-PRP antibody titres, possibly through catalytic depolymerization of PRP in the presence of aluminium hydroxide or because they lack the adjuvant effect of the whole cell pertussis component on PRP.

Another potential cause of the resurgence was the concomitant introduction of meningococcal C (MenC) conjugate vaccine in 1999, which was given at the same time as the Hib conjugated vaccine. Most of the MenC conjugate used was CRM based, and there is evidence that use of this vaccine together with DTaP-Hib also results in lower immunogenicity of the Hib component.

Control of the resurgence was achieved by the administration of a single dose of Hib vaccine to all children aged 6 months to 4 years in April 2003. In 2004, the DTwP-Hib conjugate was switched to routine use of DTaP–IPV–Hib conjugate, and a routine booster dose of Hib vaccine, administered as a Hib–MenC combination, at 12 months of age was added to the schedule in 2006. A second preschool booster campaign was conducted in 2007 for children who were too old for the 12-month booster dose but too young for the 2003 booster campaign.

Following these actions, the number of cases of invasive Hib disease declined rapidly and has remained at a very low level, with a few cases of invasive Hib disease in adults.

There was a similar resurgence in the Republic of Ireland, which had also introduced an infant Hib immunization programme with a schedule of three doses at 2, 4, 6 months without a booster dose.

The UK experience with Hib conjugate vaccines showed that immunological memory per se was insufficient to confer clinical protection. The lower-than-expected vaccine effectiveness of an early accelerated infant immunization schedule was masked for several years by the catch-up campaign which produced high levels of antibody and prolonged direct protection in older cohorts and contributed to high population immunity. Protection against Hib infection may depend on the level of serum anti-PRP antibodies at the time of acquisition of the organism in the nasopharynx. A booster dose in the second year of life produces high levels of serum anti-PRP antibodies, which are sustained above the protective threshold to provide protection against Hib infection in children <5 years of age.

19.12 Invasive *H. influenzae* Infections in Europe in the Era of Routine Hib Conjugate Vaccination

In 2018, there were 3982 cases of invasive *H. influenzae* disease reported by 30 European countries to ECDC. The overall incidence was 0.8/100,000 population (Fig. 19.6). Of these, 2266/3982 (57%) of the isolates were of known serotype; 1777/2266 (78%) were NTHi. NTHi was the most common *H. influenzae* reported in all age groups, and the majority of cases were in patients aged >65 years. There were 153 Hib reports (7%) and the majority of Hib infections occurred in older adults with underlying comorbidities. There were 44 cases of Hib infection in children aged <5 years with documented Hib vaccination status; 8 of the 21 cases aged <1 year were unvaccinated and 6 had received only one dose, while 9 of the 23 cases in children aged 1–4 years were unvaccinated.

Hif was the most common capsulated serotype with 213 (9%) reported cases. There were 63 Hie infections (3%). Both Hif and Hie infections occurred mainly in infants and older adults with underlying comorbidities. The most common presentation of NTHi, Hie and Hif infections is pneumonia, followed by sepsis. There were 60 cases reported as Hia, Hic, Hid or non-b infections.

There had been a concern that other capsulated serotypes of *H. influenzae* might occupy the ecological niche formerly occupied by Hib and emerge as significant causes of invasive disease. This has not happened although there has been a small increase in the number of invasive Hif and Hie cases in Europe. However, there has been a significant year-on-year increase in the number of cases of invasive NTHi infection. A review of the 260 invasive *H. influenzae* isolates submitted to the Portuguese Reference laboratory from 2011 to 2018 reported that the major-

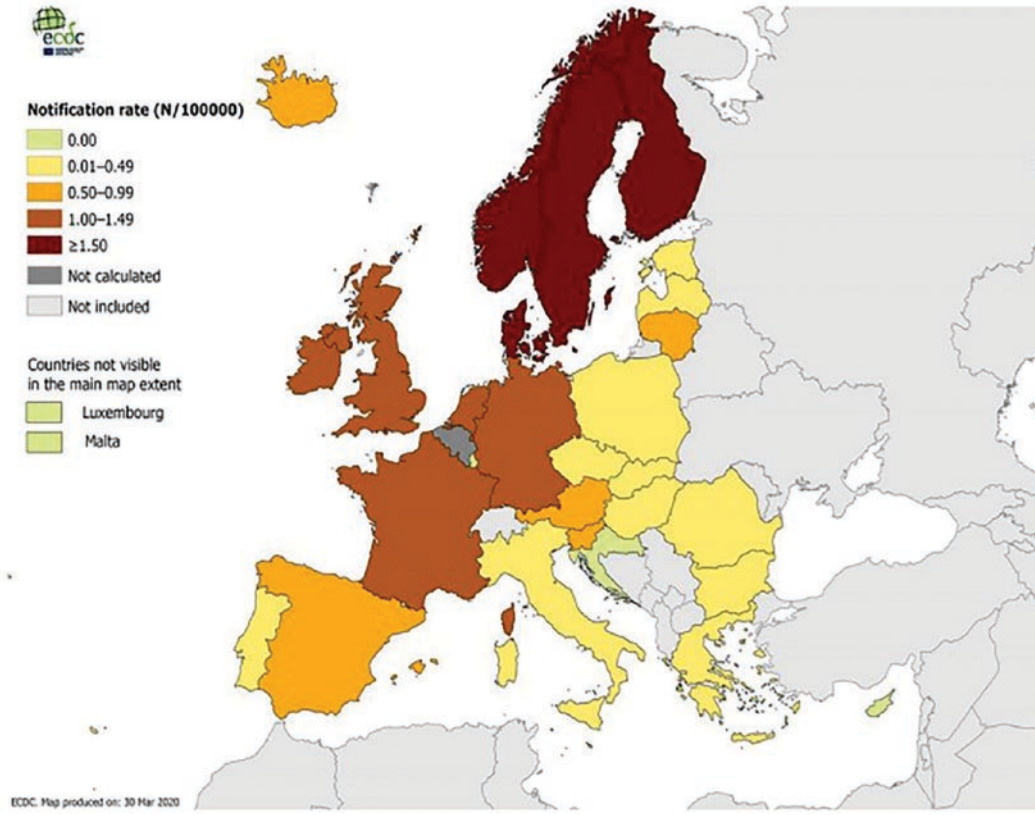


Fig. 19.6 Distribution of confirmed *Haemophilus influenzae* disease cases per 100,000 population by country, EU/EEA, 2018 Source: Country reports from Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom (Annual Epidemiological Review for 2018 – Haemophilus influenzae (europa.eu))

ity were NTHi (79%), which predominantly affected older adults (64% ≥65 years). Over half (55.6%) of the encapsulated infections occurred in preschool age children, with Hib being the most common (13.5%) followed by Hif (3.1%), Hia (2.7%) and Hie (1.5%). Nineteen of the 25 Hib infections in young children occurred in children who would have been eligible to have received two to four doses of vaccine. Hib vaccine coverage in Portugal is (~100%). A small number of Hia infections have also been reported in the UK and Italy. Data from 2017 to 2018 from four European countries (England, Germany, Italy and Finland) confirmed the predominance of NTHi infections (77–85%). Hib was the commonest encapsulated serotype in Italy (11.5%), whereas Hif was the most frequent in the other three countries.

19.13 Conclusions

The introduction of Hib conjugate vaccine has been extremely successful, with the virtual elimination of invasive Hib disease in children and a significant reduction in cases in adults due to herd protection. A small number of cases of invasive Hib disease continue to occur in Europe, mainly in adults or in unvaccinated children, with some Hib vaccine failures. The continuing circulation of Hib emphasizes the importance of maintaining high coverage of Hib vaccine and continuing surveillance to

monitor the evolution of invasive *H. influenzae* infections in Europe. NTHi have now emerged as the commonest cause of invasive *H. influenzae* infection, including pneumonia and bacteraemia. A vaccine effective against NTHi could be of value in preventing these infections. A 10-valent pneumococcal conjugate vaccine (PHid-CV; Synflorix: GSK) uses *H. influenzae* outer membrane lipoprotein D as its carrier protein, which is conserved amongst the majority of strains of *H. influenzae*. Immunization results in high concentrations of anti-protein D antibodies, but has no effect on nasopharyngeal NTHi colonization and to date has not had any demonstrable efficacy against invasive NTHi infections. The challenge is to overcome the marked heterogeneity and phase variability of NTHi. Such a vaccine could be targeted at groups who have a high incidence of mucosal NTHi infections, including otitis media in Indigenous children or adults with chronic obstructive pulmonary disease.

Bibliography

Anderson EC, Begg NT, Crawshaw SC, Hargreaves RM, Howard AJ, Slack MPE. Epidemiology of invasive *Haemophilus influenzae* infections in England and Wales in the prevaccination era (1990–2). Epidemiol Infect. 1995;115(1):89–100.

Anderson P. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. J Infect Dis. 1984;149(6):1034–5.

Collins S, Ramsay M, Campbell H, Slack MPE, Ladhani SN. Invasive *Haemophilus influenzae* type b disease in England and Wales: who is at risk after 2 decades of routine childhood vaccination? Clin Infect Dis. 2013;57(12):1715–21.

Collins S, Litt D, Almond R, Findlow J, Linley E, Ramsay M, Borrow R, Ladhani S. *Haemophilus influenzae* type b (Hib) seroprevalence and current epidemiology in England and Wales. J Infect. 2018;76:335–341.

Daum RS, Zenko CE, Given GZ, Ballanco GA, Parikh H, Germino K. Magnitude of interference after diphtheria-tetanus toxoids-acellular pertussis/ *Haemophilus influenzae* type b capsular polysaccharide-tetanus vaccination is related to the number of doses administered. J Infect Dis. 2001;184(10):1293–9.

Dagan R, Poolman JT, Zepp F. Combination vaccines containing DTPa-Hib: impact of IPV and coadministration of CRM197 conjugates. Expert Rev Vaccines. 2008;7:97–115.

Decker MD, Edwards KM, Bradley R, Palmer P. Comparative trial in infants of four conjugate *Haemophilus influenzae* type b vaccines. J Pediatr. 1992;120(2 Pt 1):184–9.

Heliodoro CIM, Bettencourt C, Bajanca-Lavado MP. Molecular epidemiology of invasive *Haemophilus influenzae* disease in Portugal: an update of the post-vaccine period, 2011–2018. Europ J Clin Microbiol Infect Dis. 2020;39:1471–1480.

Käyhty H, Peltola H, Karanko V, Mäkelä H. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. J Infect Dis. 1983;147(6):1100.

Ladhani S, Heath PT, Slack MP, McIntyre PB, Diez-Domingo J, Campos J, Dagan R, Ramsay ME. *Haemophilus influenzae* serotype b conjugate vaccine failure in twelve countries with established national childhood immunization programmes. Clin Microbiol Infect. 2010a;16(7):948–54.

Ladhani S, Slack MP, Heath PT, von Gottberg A, Chandra M, Ramsay ME. European Union Invasive Bacterial Infection Surveillance. Invasive *Haemophilus influenzae* Disease, Europe, 1996–2006. Emerg Infect Dis. 2010b;16:455–63.

Ladhani SN, Collins S, Vickers A, Litt DJ, Crawford C, Ramsay ME, Slack MPE. Invasive *Haemophilus influenzae* serotype e and f disease, England and Wales, Emerg Infect Dis. 2012;18(5):725–32.

Ladhani SN. 2012. Two decades of experience with the *Haemophilus influenzae* serotype b conjugate vaccine in the United Kingdom. Clin Ther. 34:385–99.

Peltola H, Käyhty H, Sivonen A, Mäkelä H. *Haemophilus influenzae* type b capsular polysaccharide vaccine in children: a double-blind field study of 100,000 vaccinees 3 months to 5 years of age in Finland. Pediatrics. 1977;60(5):730–7.

Peltola H. Worldwide *Haemophilus influenzae* type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. Clin Micro Rev. 2000;13(2):302–17.

Takala AK, Eskola J, Peltola H, Mäkelä H. Epidemiology of invasive *Haemophilus influenzae* type b disease among children in Finland before vaccination with *Haemophilus influenzae* type b conjugate vaccine. Pediatr Infect Dis J. 1989;8(5):297–302.

Slack M, Esposito S, Haas H, Mihalyi A Nissen M, Mukherjee P, Harrington L. *Haemophilus influenzae* type b disease in the era of conjugate vaccines: critical factors for successful eradication. Expert Rev Vaccines. 2020:19(10):903−917.

Slack MPE, Cripps AW, Grimwood K, Mackenzie GA, Ulanova M. Invasive *Haemophilus influenzae* Infections after 3 Decades of Hib Protein Conjugate Vaccine Use. Clin Microbiol Rev. 2021; 34(3):e00028-21.

Slack MPE. Long Term Impact of Conjugate Vaccines on *Haemophilus influenzae* Meningitis: Narrative Review. Microorganisms. 2021; 9(5):886. https://doi.org/10.3390/microorganisms9050886

Van Eldere J, Slack MP, Ladhani S, Cripps AW. Non-typeable *Haemophilus influenzae*, an under-recognised pathogen. Lancet Infect Dis. 2014;14(12):1281–92.

Wang S, Tafalla M, Hanssens L, Dolhain J. A review of *Haemophilus influenzae* disease in Europe from 2000 to 2014: challenges, successes and the contribution of hexavalent combination vaccines. Exp Rev Vaccines. 2017;16(11):1095–105.

Whittaker R, Economopoulou A, Dias JG, Bancroft E, Ramliden M, Celentano LP. Epidemiology of Invasive *Haemophilus influenzae* Disease, Europe, 2007–2014. Emerg Infect Dis. 2017;23(3):396–404.

WHO European Health Information Gateway. https://gateway.euro.who.int/en/indicators/hfa_611-7210-infants-vaccinated-against-invasive-disease-due-to-haemophilus-influenzae-type-b/Accessed 23.06.2021

Pediatric Combination Vaccines

Federico Martinón-Torres

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_20

20.1 Introduction: The Need, Challenges, and Benefits of Combination Vaccines

Since the beginning of the vaccination era, the number of vaccine-preventable diseases has continued to increase at a fast rate. Traditionally, with each new vaccine included in the vaccination schedule, a new injection was required to administer the immunization, and this sparked multiple responses from different social sectors: On the one hand, general practitioners were confused by the ever-changing immunization schedules; on the other hand, parents were concerned about their children becoming "pincushions." This problem, far from being solved, continued to worsen as the number of vaccines in development raised each year, making the situation more pressing.

Different approaches emerged to address the problem. One of these involved deferring additional injections until the next office visit. However, ultimately, this strategy backfired: The increasing costs and burden on staff associated with the scheduling of new visits, combined with the increased likelihood of vaccinations being missed, ended up jeopardizing vaccination coverages. In this context, the necessity for combination vaccines became acute.

Combination vaccines are individual preparations that include two or more antigens of different microorganisms. Combination vaccines have been used in adults and children alike for over half a century; in 1948, the combination of diphtheria, tetanus, and pertussis antigens into a single vaccine was first used to vaccinate infants and children. Since then, many new techniques have been developed and the number of components combined into a single product has risen greatly.

Combination vaccines have not only solved the burden of multiple injections. Other challenges such as the storage and shipment of vaccines, the increasing number of visits, the injection of more adjuvants, or the introduction of new vaccines into the calendar have been met, owing to the availability of combination vaccines (◘ Fig. 20.1).

20.2 The "Perfect" Combination Vaccine

An ideal combination vaccine needs to meet the following requirements:

- *Safety and efficacy*: A new combination vaccine should not be more reactive, less immunogenic, or less efficacious than the individual components administered separately.
- *Fit the established immunization schedule*: A combination vaccine should include components that are normally administered at the same immunization visit and respect its established timing and interval, with only slight variations being acceptable.
- *Ease of use*: From the practical point of view, a combination vaccine should be easy to store and administer, and not increase the burden on staff.

20.3 Composition of Combination Vaccines

Commonly administered combination vaccines include as base the diphtheria and tetanus toxoid, used alone (DT or Td) or with whole-cell (DTwP) or acellular (DTaP) pertussis component (◘ Fig. 20.2). To this baseline product, a plethora of components can be added. Common combinations include inactivated poliovirus (IPV), *Haemophilus influenzae b* vaccine (Hib), and/or hepatitis B vaccine (HepB). Although not commercialized to date, additional components might be meningococcal conjugate vaccine or hepatitis A vaccine (HA).

Another branch of combination vaccines is live attenuated measles–mumps–rubella vaccine (MMR), with a more recent addition of a varicella vaccine (V) component (see ▶ Chap. 9). Henceforth, this chapter focuses specifically on the pentavalent and hexavalent combination vaccines (◘ Tables 20.1 and 20.2).

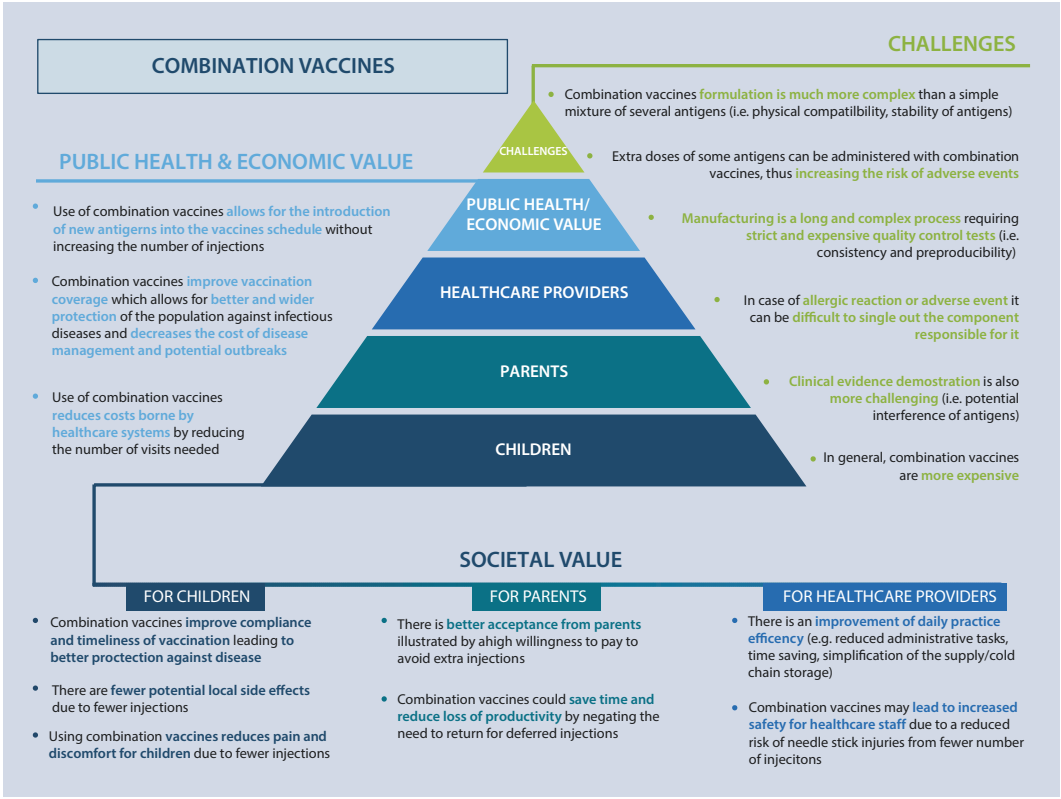


Fig. 20.1 Combination vaccines: from challenges to benefits (Adapted from Maman et al. 2015). Several key benefits from combination vaccines can be easily identified, with societal and public health and economic categories being the most important. Also, important challenges should be considered

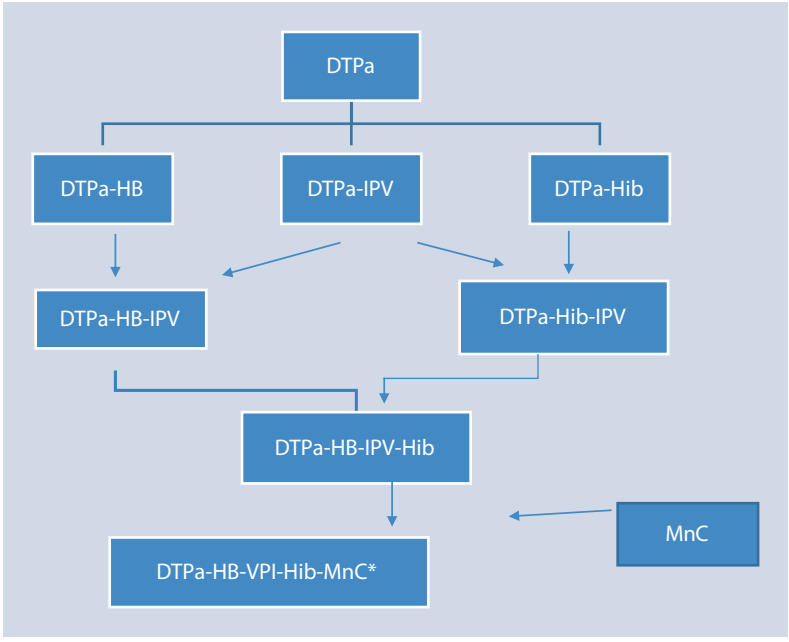


Fig. 20.2 Development of combination vaccines based on DTPa. (*)Heptavalent vaccine with MenC under development

Table 20.1 Pentavalent combination vaccines. Summary of characteristics of main pentavalent vaccines available in Europe

Combination	Commercial name	Company	DT	TT	PT (mcg)	FHA (mcg)	PRN (mcg)	FIM (mcg)	HBs (mcg)	PRP-T (mcg)	Polio 1 (D)	Polio 2 (D)	Polio 3 (D)	Adjuvants
DTPa–IPV–Hib	Pediacel®	Sanofi Pasteur	30 IU	40 IU	20	20	3	5	–	10–20	40	8	32	Aluminum phosphate
	Infanrix IPV/Hib®	GSK	30 IU	40 IU	25	25	8	–	–	10–25	40	8	32	Aluminum hydroxide, hydrated
	Pentaxim® Pentavac®	Sanofi Pasteur	30 IU	40 IU	25	25	–	–	–	10	40	8	32	Aluminum hydroxide, hydrated

DT diphtheria toxoid, *TT* tetanus toxoid, *PT* pertussis toxoid, *FHA* filamentous hemagglutinin, *PRN* pertactin, *FIM* fimbriae type 2 and 3, *HBs* hepatitis B surface antigen, *PRP-T* polyribosylribitol phosphate conjugated to tetanus toxoid, *Polio 1* poliovirus (inactivated) type 1 (Mahoney), *Polio 2* poliovirus (inactivated), type 2 (MEF-1), *Polio 3* poliovirus (inactivated) type 3 (Saukett)

Table 20.2 Hexavalent combination vaccines. Summary of characteristics of main hexavalent vaccines available in Europe

Combination	Commercial name	Company	DT (IU)	TT (IU)	PT (mcg)	FHA (mcg)	PRN (mcg)	FIM (mcg)	HBs	PRP-T[a] PRP-OMC (mcg)[b]	Polio 1/2/3 (D)	Adjuvants	Presentation
DTaP5-HB-IPV-Hib	Vaxelis®	Sanofi Pasteur and MSD	20	40	20	20	3	5	10	3 / 50 mcg[b]	40 /8 /32	Aluminum phosphate Aluminum hydroxyphosphate sulfate (0.32mg Al^{3+})	Fully liquid 0.5 mL suspension (prefilled syringe) for intramuscular injection
DtaP2-HB-IPV-Hib	Hexyon® Hexacima® Hexaxim®	Sanofi Pasteur	20	40	25	25	–	–	10	12 /22 to 36 mcg[a]	40 /8 /32	Aluminum hydroxide, hydrated (0.6 mg Al^{3+})	Fully liquid 0.5 mL suspension (prefilled syringe) for intramuscular injection
DtaP3-HB-IPV + Hib	Infanrix-Hexa®	GSK	30	40	25	25	8	–	10	10 /25 mcg[a]	40 /8 /32	Aluminum hydroxide, hydrated Aluminum phosphate (0.82 mg Al^{3+})	Powder (Hib lyophilized) and suspension for 0.5 ml suspension for intramuscular injection

DT diphtheria toxoid, *TT* tetanus toxoid, *PT* pertussis toxoid, *FHA* filamentous hemagglutinin, *PRN* pertactin, *FIM* fimbriae type 2 and 3, *HBs* hepatitis B surface antigen, *PRP-T* polyribosylribitol phosphate conjugated to tetanus toxoid, *PRP-OMC* polyribosylribitol phosphate conjugated to meningococcal protein, *Polio 1* poliovirus (inactivated) type 1 (Mahoney), *Polio 2* poliovirus (inactivated), type 2 (MEF-1), *Polio 3* poliovirus (inactivated) type 3 (Saukett)

[a]Prepared with PRP-T

[b]Prepared with PRP-OMC

20.4 Introduction to Pentavalent and Hexavalent Vaccination

With the new immunization recommendations made by the WHO, the number of routine vaccinations has grown from the initial 6 recommended EPI antigens – bacillus Calmette–Guérin, diphtheria, tetanus, pertussis, poliomyelitis, and measles – to the current 11 antigens, which additionally include HepB, Hib, pneumococcus, rotavirus, and rubella. This increase meant that the development of pentavalent and hexavalent combination vaccines fitting the routine vaccination schedules became a necessity. In this respect, Europe has taken the lead in comparison with other world regions, and routine vaccination with pentavalent and hexavalent combinations, including DTPa, Hib, HepB, and IPV, has been on European vaccination programs for more than 20 years. Since the marketing authorization of Hexavac® and Infanrix Hexa® in 2000, immunization schedules in most European countries have included hexavalent vaccines. With the introduction of combination vaccines, there has been an increase in acceptance and vaccination coverage, especially for HepB.

20.4.1 Pentavalent

1. DtaP-IPV-Hib (Pediacel®, Infanrix IPV-Hib®, Pentavac®/Pentaxim®)

   Pediacel® (Sanofi Pasteur) *is indicated for primary and booster vaccination against diphtheria, tetanus, pertussis, poliomyelitis, and invasive* Haemophilus influenzae *type b disease in infants and children from the age of 6 weeks up to the fourth birthday.*

   ► https://pdf.hres.ca/dpd_pm/00015723.PDF

   Infanrix IPV-Hib® (GSK) *is indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis, and* Haemophilus influenzae *type b disease from the age of 2 months or as booster dose in the second year of life.*

   ► https://www.medicines.org.uk/emc/medicine/28678

   Pentavac®/Pentaxim® (Sanofi Pasteur) *is indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis, and* Haemophilus influenzae *type b for primary vaccination in infants, as a booster in children who have previously received a primary vaccination with this vaccine, or a diphtheria–tetanus–whole-cell or acellular pertussis–poliomyelitis vaccine, whether mixed or not with freeze-dried conjugate Haemophilus* influenzae *type b vaccine.*

   ► http://www.medicines.ie/print-friendlydocument.aspx?documentid=4541&companyid=202

   The pentavalent combination including DTaP, IPV, and Hib is the most widely distributed and used combination in Europe. This combination vaccine is available in 15 out of 33 European countries, either as the main pillar of the routine vaccination program, or to complement vaccination recommendations where the hexavalent would add an unnecessary additional HepB dose.
2. DtaP–Hib–HepB (this combination is not available on the European market).
3. DTaP-IPV-HepB (this combination is not available on the European market).

Some European countries, especially in eastern Europe, still use DTwP-containing combination vaccines in their routine vaccination programs. The human immune responses against aP vaccines are directed against purified protein virulence factors whereas in wP vaccines, it is directed against an array of antigens of the whole bacterial cells. However, changes in effectiveness of wP have occurred without being noticed in the production or lot release process, which has not happened so far with aP vaccines. The use of wP-based vaccines makes the vaccines more affordable than their acellular pertussis counterparts, with significantly lower prices (see ► Chap. 18).

20.4.2 Hexavalent

DtaP–IPV–Hib–HepB (Infanrix Hexa®, Vaxelis®, Hexyon/Hexacima/Hexaxim®)

- **INFANRIX Hexa® (GSK)**

► http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000296/WC500032505.pdf

- **Hexyon®, Hexacima®, Hexaxim® (Sanofi Pasteur)**

► http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002702/WC500145808.pdf

- **Vaxelis® Sanofi Pasteur and MSD**

► http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003982/WC500202435.pdf

Four hexavalent vaccines have been licensed in Europe in the last 20 years and Europe has been the first region in the world to adopt hexavalent vaccines as part of the routine immunization program. As many as 22 out of 33 European countries routinely use vaccines combining antigens of six different diseases in children (◘ Table 20.3).

Immune responses to the diphtheria, tetanus, and polio components of the different hexavalent combinations are noninferior to those of the separate components. Although there is no serological correlate of protection against pertussis disease, the clinical efficacy of Infanrix® Hexa against pertussis has been demonstrated in household contact studies, and the more recent hexavalent vaccines have shown to achieve comparable seroprotective titers for the shared antigens. However, potentially clinically relevant differences in immune responses to vaccine antigens were observed. Hexyon®, Infanrix Hexa®, and Vaxelis® include 2, 3, and 5 pertussis antigens, respectively, with pertussis toxoid and filamentous hemagglutinin common to the three formulations (see ► Chap. 18). Anti-filamentous hemagglutinin (FHA) from pertussis and anti-polyribosylribitol phosphate (PRP) from Hib antibody concentrations tended to be higher, and anti-HBV and anti-pertussis toxin (PT) from pertussis antibody concentrations lower, in Hexyon® versus Infanrix Hexa® vaccinees. Anti-PT and anti-PRP antibody concentrations tended to be higher, and anti-HBV, anti-FHA, and anti-PRN antibody concentrations lower, in Vaxelis® versus Infanrix Hexa® vaccinees.

A fourth hexavalent vaccine, Hexavac®, was withdrawn in 2005 because of rapid waning of antibody titers against Hep B component. Currently available hexavalent vaccines induce comparable immune responses to Hep B. Infanrix® Hexa and Vaxelis® contain the same HepB component as used in the monovalent vaccines Engerix-B® and HBVaxPro®, respectively, with a different dose compared with Hexavac®. The three hexavalent vaccines use recombinant DNA technology for B hepatitis antigen production in yeast: Infanrix Hexa® and Vaxelis® use *Saccharomyces cerevisiae*, whereas Hexyon® produces it in *Hansenula polymorpha* cells.

While Vaxelis® and Hexyon® are fully liquid, ready-to-use vaccines, Infanrix® Hexa requires reconstitution before administration. Data regarding the long-term persistence of immune response, immune memory, and vaccine effectiveness of Vaxelis® and Hexyon® are still needed as compared with Infanrix® Hexa.

20.5 Practical Considerations

20.5.1 Concomitant Administration with Other Vaccines

DTaP combination vaccines may be given at the same time as pneumococcal conjugate, rotavirus, meningococcal conjugate and measles, mumps, rubella, and varicella vaccines. The potential for the interaction of DTaP-based penta- and hexavalent vaccines with these four vaccines has been studied in sever-

Table 20.3 Use of pentavalent and hexavalent vaccines in immunization schemes in Europe

	Countries	DTPa, VPI, Hib		HepB		Hexavalent	Pentavalent
		Priming age (months)	Booster age (months)	Universal	Schedule (months)	Use (months)	DTPa, VPI, Hib (months)
2 + 1	Austria	3, 5	12	Yes	3, 5, 12	3, 5, 12	No
	Italy		11–13	Yes	3, 5, 11	3, 5, 11	No
	Iceland		12	No	–	No	3, 5, 12
	Denmark		12	No, RG only	–	3, 5, 12	3, 5, 12
	Finland		12	No, RG only	–	No	3, 5, 12
	Czech Republic		11-13	Yes	3, 5, 11	3, 5, 11	No
	Netherlands		11	Yes	3, 5, 11	3, 5, 11	No
	Norway		12	Yes	3, 5, 12	3, 5, 12	No
	Sweden		12	Yes	3, 5, 12	3, 5, 12	No
	Slovenia		11-18	Yes	3, 5, 11-18	3, 5, 11-18	No
	Slovakia	2, 4	10	Yes	2, 4, 10	2, 4, 10	No
	France		11	Yes	2, 4, 11	2, 4, 11	No
	Spain		11	Yes	2, 4, 11	2, 4, 11	No
	Romania		11	Yes	2, 4, 11	2, 4, 11	No

3 + 1	Greece	2, 4, 6	15–18	Yes	2, 4, 6–18	2, 4, 6–18	No
	Ireland		13 (Hib)	Yes	2, 4, 6	2, 4, 6	No
	Portugal		18 (DTPa, Hib)	Yes	0, 2, 6	No	2, 4, 6
	Lithuania		18	Yes	0, 1, 6	No	2, 4, 6, 18
	Latvia		12–15	Yes	2, 4, 6, 12–15	2, 4, 6, 12–15	2, 4, 6
	Cyprus		15–18	Yes	2, 4, 8–12	No	2, 4, 6, 15–18
	Croatia		15–18	Yes	2, 4, 15–18	2, 4/6, 15-18	4/6
	Switzerland		15–24	No	1, 6, 15–24	No	2, 4, 6, 15–24
	Germany	2, 3, 4	11–14	Yes	2, 3, 4, 11–14	2, 3, 4, 11–14	2, 3, 4, 11–14
	Belgium		15	Yes	2, 3, 4, 15	2, 3, 4, 15	No
	Luxembourg		13	Yes	2, 3, 13	2, 3, 13	4
	UK		12–13 (Hib/MenC)	No, RG only	–	8, 12 and 16 weeks	No
	Malta		18	Yes	12, 13, 18	No	2, 3, 4, 18
	Hungary		18	Yes	Over 10 years	No	2, 3, 4, 18
	Bulgaria		16	Yes	0, 1, 6 (monovalent) or 2, 3, 4 (with hexavalent)	2, 3, 4	(2, 3, 4), 16
	Estonia	3, 4–5, 6	24	Yes	3, 4–5, 6	3, 4–5, 6	No
	Poland	2, 4, 5-6	16 (DTPw, VPI, Hib)	Yes	0, 2, 7	No	No

Data compiled in January 2021 ► https://vaccine-schedule.ecdc.europa.eu/
RG risk groups

alwclinical trials, and no important variations in the antibody titers were found.

20.5.2 Interchangeability

Monovalent vaccines and combination vaccines for the same diseases produced by the same manufacturer usually carry similar antigens, with no issues regarding interchange of vaccines. Questions arise, however, between hexavalent vaccines manufactured by different companies.

Several studies have addressed interchangeability and shown that vaccines containing diphtheria, tetanus, poliovirus, HepB, and Hib antigens are generally interchangeable. As there is no serological correlation of protection for pertussis, the interchangeability for those vaccines containing pertussis antigens has remained unclear for a long time. Owing to this, recommendations state that whenever possible, it would be preferable to use the same manufacturer's vaccine, at least for priming, but no contraindication has been stated against the opposite procedure. A number of studies have shown that combining aP-containing vaccines from different manufacturers regardless of the immunization schedule will provide similar seroprotective levels and immune memory as if they were the same vaccine.

In general, it is always preferable to use the same vaccine, at least in the priming schedule. Only if the timeliness of the immunization of the child can be affected, or if the vaccine administered previously is unknown, vaccination with vaccines containing similar antigens is not contraindicated.

20.5.3 Vaccination Schedules

In general, the schedules regarding pentavalent/hexavalent vaccines used in Europe can be summarized as either 2 + 1 or 3 + 1. Both schedules have proved to be effective for pentavalent and hexavalent vaccines. The specific schedules of the available hexavalent vaccines according to their label are summarized in Table 20.4.

Table 20.4 Posology specified in the summary of product characteristics of the different hexavalent vaccines available

	Full-term infants		Preterm infants >24 weeks		HepB at birth
	Primary vaccination (minimum 6 weeks old)	Booster vaccination	Primary vaccination	Booster vaccination	
Infanrix® Hexa	3-dose (at least 1-month intervals between doses)	At least 6 months after priming and preferably before 18 months[a]	3-dose (at least 1-month intervals between doses)	At least 6 months after priming and preferably before 18 months	
	2-dose (at least 2-month intervals between doses)	At least 6 months after priming and preferably before 11–13 months[a]			

Table 20.4 (continued)

	Full-term infants		Preterm infants >24 weeks		HepB at birth
Hexyon®	3-dose (at least 1-month intervals between doses)	At least 6 months after priming[b]	No data available		In the absence of hepatitis B vaccination at birth, it is necessary to give a hepB vaccine booster dose Hexavalent vaccines can be considered for HepB booster dose When a hepB vaccine is given at birth, hexavalent vaccines can be used as replacement for supplementary HepB doses after week 6. If a second dose of HepB is required before this age, a monovalent hepB vaccine should be used.
	2-dose (at least 2-month intervals between doses)	At least 6 months after priming[b]			
Vaxelis®	3-dose (at least 1-month intervals between doses)	At least 6 months after priming[c]	Can be given	Can be given	In the absence of hepatitis B vaccination at birth, it is necessary to give a hepB vaccine booster dose Hexavalent vaccines can be considered for HepB booster dose When a hepB vaccine is given at birth, hexavalent vaccines can be used as replacement for supplementary HepB doses after week 6. If a second dose of HepB is required before this age, a monovalent hepB vaccine should be used
	2-dose (at least 1-month intervals between doses)	At least 6 months after priming[c]	Can be given	Can be given	

[a]Not after 36 months old
[b]Not after 24 months old
[c]Not after 15 months old

20.6 Concerns and Issues of a Lifetime with Combination Vaccines

20.6.1 Multiple Antigens and Immunity Overload

As the number of antigens administered to infants has kept growing, some parents and also healthcare professionals have expressed concerns about a possible overload of the immune system of children. This theory has been widely discussed and convincingly refuted, but misguided concerns still populate the internet. Children are commonly exposed to many more antigens in daily life than those injected in the vaccines, with no negative impact on the immune system.

20.6.2 Hexavalent Vaccine Safety and Their Relation to Sudden Unexpected Death

An association between hexavalent vaccination and the occurrence of sudden unexpected death (SUD) was suspected when a series of three SUDs were reported in Germany within 48 h of the administration of the booster dose of Hexavac® between 2000 and 2003. Standardized mortality ratios for SUD cases within 1 day of vaccination were 31.3 (95% CI 3.8–113.1; 2 cases observed; 0.06 cases expected), and 23.5 within 2 days of vaccination (95% CI 4.8–68,6; 3 cases observed; 0.13 cases expected), so even when these data did not prove a causal relationship, an alarm signal was raised, and further investigation began. The Committee for Proprietary Medicinal Products (CPMP) issued a statement in 2003 after a statistical analysis based on the German data, and found no plausible biological cause for association between hexavalent vaccines and SUD in the second year of life.

In Italy, a case series studying neonates born in the period 1999–2004 reported that the association between hexavalent vaccine administration and risk of SUD in the first 14 days after vaccine administration was significantly lower than that estimated in Germany; the authors claimed that this association was limited to the first vaccine dose only, at an age coinciding with the highest incidence of SUD. Relative risk in the first 2 days after vaccination was 0.7 and 2.3 for Hexavac® and Infanrix® Hexa, respectively; the risk was 2.8 versus 1.4 and 1.6 versus 1.5 for the first week and for the 2 weeks after vaccine administration, respectively. Based on these data, it was concluded that the limited increase in relative risk appeared to be confined to the first dose, and that it may be partially explained by the confounding effect of age.

Other studies performed so far have confirmed that none of the hexavalent vaccines used at the moment had any distinct effect on SUD. Currently, a family history of SUD does not contraindicate the use of hexavalent vaccines.

20.6.3 Reduced Hib Response When Combined with DTaP

The most commonly reported example of immune interference in DTaP-based combination vaccines is the reduction in antibody titers to the Hib component of the vaccine polyribosylribitol phosphate (PRP) antigen. wP-based vaccines do not show this interference to the same extent, as the wP component may be acting as an adjuvant.

An interference between tetanus toxoid (TT) and Hib has been demonstrated. In Hib vaccines, TT acts as a carrier protein conjugated to the PRP. Several reasons for this interference have been mentioned: Competition between TT-specific and PRP-specific B cells for the Hib conjugate antigen, suppression of PRP response by clonal expansion of TT-specific B cells, and physical prevention of the binding between the conjugate antigen and PRP-specific B cells by the TT carrier protein. FHA has also been proven to interact with PRP. Studies show that FHA is a suppressor of IL12 and IFNγ, suppressing immune responses to co-injected antigens. Lastly, aluminum hydroxide has been reported to be incompatible with Hib, with 5–11 times lower levels of PRP antibodies.

Whatever the case, this lower response does not seem to have a clinical impact. It has been stated that the current seroprotective threshold against PRP is probably too high, and that antibody responses below this threshold are similarly protective. Furthermore, the newest hexavalent vaccine combines PRP with meningococcal outer membrane protein (PEP-OMPC), which is known to elicit a stronger early immunogenic response against Hib than the PRP-T antigen.

20.6.4 Combining with Neonatal Hepatitis B Immunization

In the case of hepatitis B, several countries administer the first dose at the time of birth, as recommended by the WHO. The other components of the combination vaccine are not to be administered in the first days of life and a

combination of HepB and DTaP still requires administration of monovalent HepB at birth followed by doses in combination with DTaP at 2, 4, and 6 months, resulting in an unnecessary fourth dose of HepB at the 6th month. A study comparing the DTaP–HepB combination administered at 2, 4, and 6 months with separate administration of HepB at birth, 1, and 6 months and DTaP at 2, 4, and 6 months showed significantly lower HepB antibody titers with the combination vaccine. However, antibody levels were still above serologically recognized levels of protection in 99% of the subjects. Furthermore, administration of a DtaP–HepB–IPV/Hib vaccine at 2, 4, and 6 months after a dose of HepB vaccine shortly after birth did not have an impact on protective anti-HBs titers and was not more reactogenic than the same combination given without the birth dose of HepB.

20.6.5 HepB Reduction in Long-Term Protection

Rapid waning of hepatitis B vaccine–induced antibodies was the reason for the withdrawal of the hexavalent combination vaccine, Hexavac®, by the EMEA in 2005. Although >95% of children vaccinated with Hexavac® had seroprotective antibody levels after primary vaccination, up to 20% of them were relatively low (≤100 IU/L) and these subjects had a lower response to the booster dose. This observation was also reflected in studies where Hexavac® was co-administered with pneumococcal vaccine or meningococcus C conjugate vaccine. It was assumed that these children might not have assured protection against hepatitis B during adolescence and adulthood. This theory notwithstanding, no increase in hepatitis B infection has been recorded in those countries where Hexavac® was widely used. In a subsequent study, Zanetti et al. showed that even though 60% of the 5- to 6-year-old children studied did not have seroprotective levels against HepB before the booster dose, a protective antibody response was induced in 92.1% of the participants after booster dose administration. The authors concluded that Hexavac®-vaccinated children maintained T-cell memory and were able to trigger anti-HB production by B cells when exposed to the viral antigen.

At the same time, it has been shown that vaccine dosage and the length of the gap between the last and preceding doses in the primary series are the main determinants of immune persistence in HepB vaccination. The new generation of hexavalent vaccines contain increased amounts of hepB to avoid this issue.

20.6.6 Shortage Acellular Pertussis Component

Starting in 2015, there was a shortage in the pertussis acellular component of the combination vaccines in Europe, owing to reduced production capacities. This situation affects not only acellular pertussis vaccines, but also all the combination vaccines containing this component.

Europe has issued some recommendations to modify the immunization calendars of those countries enduring the shortage. Priority should be given in the following order:

- The infant primary immunization series (first year of life).
- The first toddler booster (second year of life) dose.
- If applicable, the first toddler booster dose should be prioritized over the school-entry booster.
- Eventually, the use of a low-antigen-content pertussis vaccine as a preschool booster, instead of a regular-dose vaccine, while vaccinating these cohorts at a later age.

In countries where vaccination during pregnancy is recommended and Tdap vaccine is in short supply, it is suggested that doses should be preserved for maternal immunization, instead of adolescent or preschool booster doses, since maternal immunization directly benefits newborns.

As an example, Spain has had to adjust its immunization schedule as a result of the

shortage. Following the rise in demand for Tdap vaccines resulting from the start of the vaccination program in pregnant women against pertussis, it has been decided to temporarily withdraw the booster dose indicated for 6-year-old children to preserve these pertussis-containing vaccine doses for primary vaccination, booster dose. In addition, hexavalent vaccine is now administered in a 2 + 1 schedule.

20.6.7 Pertussis Components and Immunity Waning

The main components of the aP pertussis vary between different vaccines and include PT, FHA, PRN, and Fimbriae type 2 and 3 (FIM). Numerous formulations have been developed that differ in the number, type, and quantity of antigens, purification, and detoxification methods. Only the PT component is deemed essential for conferring protection against pertussis infection, as demonstrated for example in Denmark, where a monovalent pertussis vaccine containing only PT has been in use for more than 20 years, with no pertussis outbreak since 2002. Results with this monovalent vaccine are likely to be related to the more conservative detoxified method used (hydrogen peroxide), different to the agents used in the more commonly available combination vaccines. The inclusion of other antigens is expected to induce a broader immune response compared to one-component vaccines that target only PT. The clinical value of antibodies against different bacterial antigens is under investigation and it is currently unclear which bacterial targets may offer the best clinical advantage. Recent studies have addressed the importance of FIM2 and FIM3 in protecting against pertussis infection. High levels of IgG anti-Fim2/3 ≥ 5 EU/ml reduced short-term risk of pertussis in small children. These observations, along with the fact that *B. pertussis* seems to express both FIM2 and FIM3 during infection, suggest that including these two additional components in the vaccine could yield better short- and long-term protection against pertussis. Regardless of the inclusion or exclusion of the different components, no inferiority in immune response, duration of immunity, efficacy, or safety has been reported in any of the commercialized DTaP combination vaccines.

Further Reading

Aristegui J, Dal-Re R, Diez-Delgado J, et al. Comparison of the reactogenicity and immunogenicity of a combination diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio (DTPa-HBV-IPV) vaccine, mixed with the *Haemophilus influenzae* type b (Hib) conjugate vaccine and administered as a single injection, with the DTPa-IPV/Hib and hepatitis B vaccines administered in two simultaneous injections to infants at 2, 4 and 6 months of age. Vaccine 2003;21:3593–600.

Carlsson RM, Claesson BA, Selstam U, Fagerlund E, Granström M, Blondeau C, Hoffenbach A. Safety and immunogenicity of a combined diphtheria-tetanus-acellular pertussis-inactivated polio vaccine-Haemophilus influenzae type b vaccine administered at 2-4-6-13 or 3-5-12 months of age. Pediatr Infect Dis J 1998;17(11):1026–33.

Chiappini E, Petrolini C, Caffarelli C, Calvani M, Cardinale F, Duse M, Licari A, Manti S, Martelli A, Minasi D, Miraglia Del Giudice M, Pajno GB, Pietrasanta C, Pugni L, Tosca MA, Mosca F, Marseglia GL. Hexavalent vaccines in preterm infants: an update by Italian Society of Pediatric Allergy and Immunology jointly with the Italian Society of Neonatology. Ital J Pediatr. 2019;45(1):145. doi: https://doi.org/10.1186/s13052-019-0742-7. PMID: 31744514; PMCID: PMC6862761.

Decker MD. Principles of pediatric combination vaccines and practical issues related to use in clinical practice. Pediatr Infect Dis J 2001;20(11 Suppl):S10–8.

Dewan KK, Linz B, DeRocco SE, Harvill ET. Acellular Pertussis Vaccine Components: Today and Tomorrow. Vaccines (Basel) 2020;8(2):217. doi: https://doi.org/10.3390/vaccines8020217

Dolhain J, Janssens W, Mesaros N, Hanssens L, Fierens F. Hexavalent vaccines: increasing options for policy-makers and providers. A review of the data supporting interchangeability (substitution with vaccines containing fewer antigens) and mixed schedules from the same manufacturer. Expert Rev. Vaccines. 2018;17(6):513-524. doi: https://doi.org/10.1080/14760584.2018.1419070.

Dolhain J, Janssens W, Sohn WY, Dindore V, Mukherjee P. Integration of hexavalent diphtheria, tetanus, acellular pertussis, hepatitis B virus, inactivated poliomyelitis and Haemophilus influenzae type b conjugate vaccine within existing national rec-

ommendations following a birth dose of monovalent hepatitis B virus vaccine: results of a systematic review in the Asia Pacific region. Expert Rev Vaccines 2019;18(9):921−933. doi: https://doi.org/10.1080/14760584.2019.1646643.

ECDC. Shortage of acellular pertussis-containing vaccines and impact on immunisation programmes in the EU/EEA. http://ecdc.europa.eu/en/publications/Publications/RRA-shortage-of-aP-containing-vaccines.pdf

Eskola J, Olander RM, Hovi T, Litmanen L, Peltola S, Käyhty H. Randomised trial of the effect of coadministration with acellular pertussis DTP vaccine on immunogenicity of Haemophilus influenzae type b conjugate vaccine. Lancet 1996;348(9043):1688–92.

Eskola J, Ward J, Dagan R, Goldblatt D, Zepp F, Siegrist CA. Combined vaccination of Haemophilus influenzae type b conjugate and diphtheria tetanus pertussis containing acellular pertussis. Lancet 1999;354:2063–8.

Esposito S, Tagliabue C, Bosis S, Ierardi V, Gambino M, Principi N. Hexavalent vaccines for immunization in paediatric age. Clin Microbiol Infect 2014;20(Suppl 5):76–85.

Lee AW, Jordanov E, Boisnard F, Marshall GS. DTaP5-IPV-Hib-HepB, a hexavalent vaccine for infants and toddlers. Expert Rev Vaccines 2017;16(2):85–92.

Mallet E, Belohradsky BH, Lagos R, Gothefors L, Camier P, Carrière JP, Kanra G, Hoffenbach A, Langue J, Undreiner F, Roussel F, Reinert P, Flodmark CE, Stojanov S, Liese J, Levine MM, Muñoz A, Schödel F, Hessel L, Hexavalent Vaccine Trial Study Group. A liquid hexavalent combined vaccine against diphtheria, tetanus, pertussis, poliomyelitis, Haemophilus influenzae type B and hepatitis B: review of immunogenicity and safety. Vaccine 2004;22(11–12):1343–57.

Maman K, Zöllner Y, Greco D, Duru G, Sendyona S, Remy V. The value of childhood combination vaccines: from beliefs to evidence. Hum Vaccin Immunother 2015;11(9):2132–41.

Marshall GS, Adams GL, Leonardi ML, Petrecz M, Flores SA, Ngai AL, Xu J, Liu G, Stek JE, Foglia G, Lee AW. Immunogenicity, safety, and tolerability of a hexavalent vaccine in infants. Pediatrics 2015;136(2):e323–32. doi:https://doi.org/10.1542/peds.|2014-4102.

Martinón-Torres F, Boisnard F, Thomas S, Sadorge C, Borrow R. PRI02C study group. Immunogenicity and safety of a new hexavalent vaccine (DTaP5-IPV-HB-Hib) administered in a mixed primary series schedule with a pentavalent vaccine (DTaP5-IPV-Hib). Vaccine 2017;35(30):3764–72. doi: https://doi.org/10.1016/j.vaccine.2017.05.043. Epub 2017 Jun 2.

Martinón-Torres F, Diez-Domingo J, Feroldi E, Jordanov E, B'Chir S, Da Costa X. Evaluation of a Hexavalent-Pentavalent-Hexavalent Infant Primary Vaccination Series Followed by a Pentavalent Booster Vaccine in Healthy Infants and Toddlers. Pediatr Infect Dis J 2019;38(3):317-322. doi: https://doi.org/10.1097/INF.0000000000002231.

Nunes MC, Madhi SA. Review of a new fully liquid, hexavalent vaccine: Hexaxim. Expert Opin Biol Ther 2013;13(4):575–93. doi: https://doi.org/10.1517/14712598.2013.774368.

Obando-Pacheco P, Rivero-Calle I, Gómez-Rial J, Rodríguez-Tenreiro Sánchez C, Martinón-Torres F. New perspectives for hexavalent vaccines. Vaccine 2018;36(36):5485-5494. doi: https://doi.org/10.1016/j.vaccine.2017.06.063. Epub 2017 Jul 1. PMID: 28676382.

Obando-Pacheco P, Rivero-Calle I, Raguindin PF, Martinón-Torres F. DTaP5-HBV-IPV-Hib pediatric hexavalent combination vaccine for use in children from 6 weeks through to 4 years of age. Expert Rev Vaccines 2019;18(11):1115-1126. doi: https://doi.org/10.1080/14760584.2019.1690457. Epub 2019 Dec 10. PMID: 31697185.

Omeñaca F, Vázquez L, Garcia-Corbeira P, Mesaros N, Hanssens L, Dolhain J, Gómez IP, Liese J, Knuf M. Immunization of preterm infants with GSK's hexavalent combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type b conjugate vaccine: A review of safety and immunogenicity. Vaccine 2018;36(7):986-996. doi: https://doi.org/10.1016/j.vaccine.2018.01.005. Epub 2018 Jan 12.

Orsi A, Azzari C, Bozzola E, Chiamenti G, Chirico G, Esposito S, Francia F, Lopalco P, Prato R, Russo R, Villani A, Franco EHexavalent vaccines: characteristics of available products and practical considerations from a panel of Italian experts. J Prev Med Hyg. 2018;59(2):E107−E119. PMID: 30083617; PMCID: PMC6069402.

Skibinski DA, Baudner BC, Singh M, O'Hagan DT. Combination vaccines. J Global Infect Dis 2011;3(1):63–72.

Syed YY. DTaP-IPV-HepB-Hib Vaccine (Hexyon®): An Updated Review of its Use in Primary and Booster Vaccination. Paediatr Drugs. 2019;21(5):397−408. https://doi.org/10.1007/s40272-019-00353-7. Erratum in: Paediatr Drugs. 2019;21(6):501

Syed YY. DTaP5-HB-IPV-Hib Vaccine (Vaxelis®): a review of its use in primary and booster vaccination. Paediatr Drugs 2017;19(1):69–80. doi: https://doi.org/10.1007/s40272-016-0208-y.

Thollot F, Scheifele D, Pankow-Culot H, Cheuvart B, Leyssen M, Ulianov L, Miller JM. A randomized study to evaluate the immunogenicity and safety of a heptavalent diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, haemophilus influenzae b, and meningococcal serogroup C combination vaccine administered to infants at 2, 4 and 12 months of age. Pediatr Infect Dis J 2014;33(12):1246–54.

Vennemann MM, Butterfass-Bahloul T, Jorch G, Brinkmann B, Findeisen M, Sauerland C, Bajanowski T, Mitchell EA, GeSID Group. Sudden infant death syndrome: no increased risk after immunisation. Vaccine 2007;25(2):336–40.

Vesikari T, Becker T, Vertruyen AF, Poschet K, Flores SA, Pagnoni MF, Xu J, Liu GF, Stek JE, Boisnard F, Thomas S, Ziani E, Lee AW. A Phase III randomized, double-blind, clinical trial of an investigational hexavalent vaccine given at two, three, four and twelve months. Pediatr Infect Dis J 2017a;36(2):209–15. doi: https://doi.org/10.1097/INF.0000000000001406.

Vesikari T, Borrow R, Da Costa X, Richard P, Eymin C, Boisnard F, Lockhart S. Concomitant administration of a fully liquid, ready-to-use DTaP-IPV-HB-PRP-T hexavalent vaccine with a meningococcal serogroup C conjugate vaccine in infants. Vaccine 2017b;35(3):452–8. doi: https://doi.org/10.1016/j.vaccine.2016.11.053.

Wang S, Tafalla M, Hanssens L, Dolhain J. A review of Haemophilus influenzae disease in Europe from 2000-2014: challenges, successes and the contribution of hexavalent combination vaccines. Expert Rev Vaccines 2017;16(11):1095−1105. doi: https://doi.org/10.1080/14760584.2017.1383157. Epub 2017 Oct 3. PMID: 28971707.

Zepp F, Schmitt HJ, Cleerbout J, Verstraeten T, Schuerman L, Jacquet JM. Review of 8 years of experience with Infanrix Hexa (DTPa-HBV-IPV/Hib hexavalent vaccine). Expert Rev Vaccines 2009;8(6):663–78.

Pneumococcal Vaccines

Ron Dagan and Shalom Ben-Shimol

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_21

21.1 Burden of Pneumococcal Disease

Streptococcus pneumoniae (Pnc) is a major cause of morbidity and mortality in children and the elderly worldwide. When classified by its polysaccharide capsule, Pnc has >95 serotypes, each capable of causing disease. However, the invasiveness varies by serotypes. Diseases caused by pneumococcus include severe infections, such as meningitis and bacteremia (both regarded as invasive pneumococcal disease; IPD), pneumonia, and other milder mucosal diseases, such as middle ear infection (otitis media) and sinusitis.

21.2 IPD: Bacteremia, Bacteremic Pneumonia, Meningitis, and Other IPDs

The highest IPD incidence occurs in children <2 years old. National pneumococcal surveillance programs are conducted in a number of countries in Europe, mainly in western countries, but also in Central and Eastern Europe (such as Croatia, Czech Republic, Hungary, Poland, Romania, and Slovakia) and in Israel. It was stated that in Europe, before widespread pneumococcal conjugate vaccine (PCV) immunization, the overall mean annual incidence of IPD in children aged <2 years was 44.4/100,000, and the mean case fatality rate for IPD was 3.5%. It is clear that figures vary between countries and populations and are largely dependent, beyond true differences, on epidemiological methods and reporting. Thus, for example, the rates reported for children <2 years, were approximately 15 cases per 100,000 in Germany and the Netherlands, but >90 and 104 per 100,000 in Spain and in Belgium, respectively. Furthermore, considerable differences in IPD rates were noted comparing different studies conducted even in the same country (Table 21.1). Overall,

Table 21.1 Annual incidence per 100,000 of invasive pneumococcal disease (IPD) in children <2 years old in Europe, pre-pneumococcal conjugate vaccine (PCV)

Country	Age (years)	Mean IPD incidence	Year
Austria	<2	14.5	2001–2003
Belgium	<2	104.4	2002–2003
Denmark	<2	43	1995–1999
Denmark	<2	50.9	2000–2005
Finland	<2	45.3	1985–1989
Germany	<2	16	1997–1998
Germany	<2	16.3	1997–2000
Hungary	2	12.5	2002–2004
Israel	<2	68.3	1993–1997
Israel	<2	77.4	1998–2002
Israel	<2	92.0	2003–2007
Italy	<2	11.3	2001–2002
Norway	<2	18.6	2001
Norway	<2	50	2000–2005
Poland	<2	19	2003–2004
Portugal	1	11.5	1999–2001
Slovenia	0–1	56.9	1993–2001
Spain	<1	110.2	1998–2001
Spain	<2	32.4	1997–2001
Spain	<2	48.4	1999–2001
UK	<2	17.2	1995–1997
UK	<2	37.8	1980–1999

Adapted from Isaacman et al. (2010)

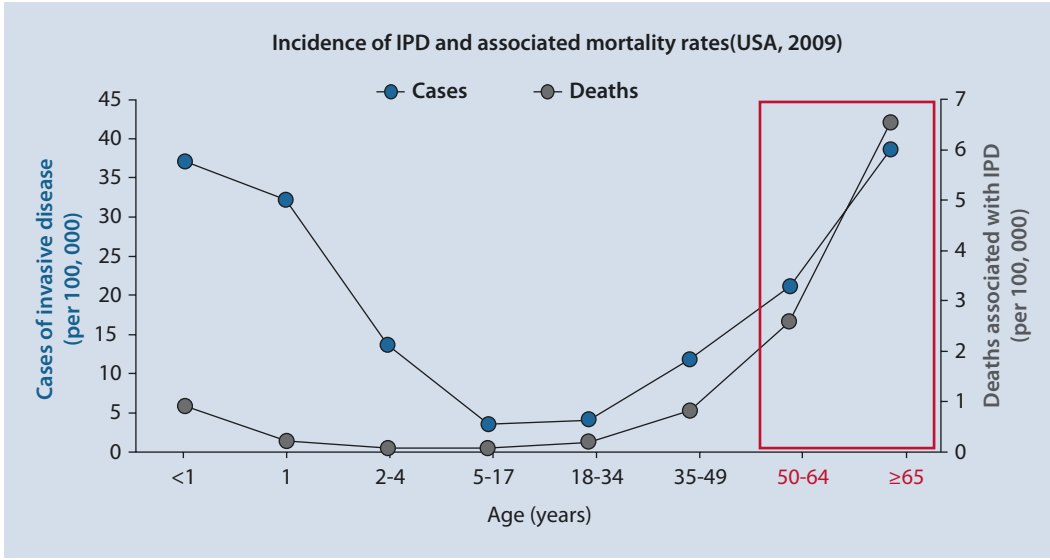


Fig. 21.1 Invasive pneumococcal disease (*IPD*) burden. *IPD* invasive pneumococcal disease, *CDC* ► http://www.cdc.gov/abcs/reports-finding/survreports/spneu09.html

in Europe, age-specific IPD rates were highest in those aged 65 years and over (13.8 cases per 100,000 population), followed by infants under 1 year of age (11.3 cases per 100,000 of the population). ► http://ecdc.europa.eu/en/healthtopics/pneumococcal_infection/Pages/Annual-epidemiological-report-2016.aspx#sthash.53mozZJI.dpuf

Globally, in the pre-PCV era, pneumococcal infections cause ~11% of all deaths in children aged <5 years, mainly from pneumonia, reaching ~500,000 deaths annually. The pneumococcal vaccine could have the potential to reduce deaths from pneumonia and the impact on mortality could potentially be greater than that from the prevention of IPD in developed countries (Fig. 21.1), where hospitalization for pneumonia and the use of medical services for otitis media (OM) in young children constitute a considerable economic burden, particularly among the very young population (<5 years old).

Pneumococcal nasopharyngeal (NP) carriage precedes disease and is the source of pneumococcal spread in the community. Carriage rates are highest during early childhood, and thus not only pneumococcal disease rates peak in young children, but these children are also the main source of Pnc spread.

Carriage rates vary considerably across Europe, and can be influenced by several factors, including the age of the population sampled, concomitant diseases, daycare center attendance, number of siblings, antibiotic usage, and the introduction and uptake of vaccines. In general, studies conducted in European crowded populations or in daycare centers show higher carriage rates.

The likelihood of *S. pneumoniae* causing disease depends upon several factors, including the invasiveness of the strains, the host susceptibility, and the existence of preceding or concurrent viral infection. Transmission of pneumococcus occurs mainly through direct and indirect contacts with respiratory secretions from patients and healthy carriers. In most cases, the individual is transiently and asymptomatically colonized. However, occasionally, pneumococci can spread from the nasopharynx to cause mucosal disease, such as otitis media (by aspiration to the middle ear fluid through the Eustachian tube), sinusitis, and pneumonia (by *S. pneumoniae* aspiration to the lungs), or by direct invasion to the bloodstream, resulting in IPD, i.e., bacteremia (in some cases, sepsis), bacteremic pneumonia, and meningitis (Fig. 21.2).

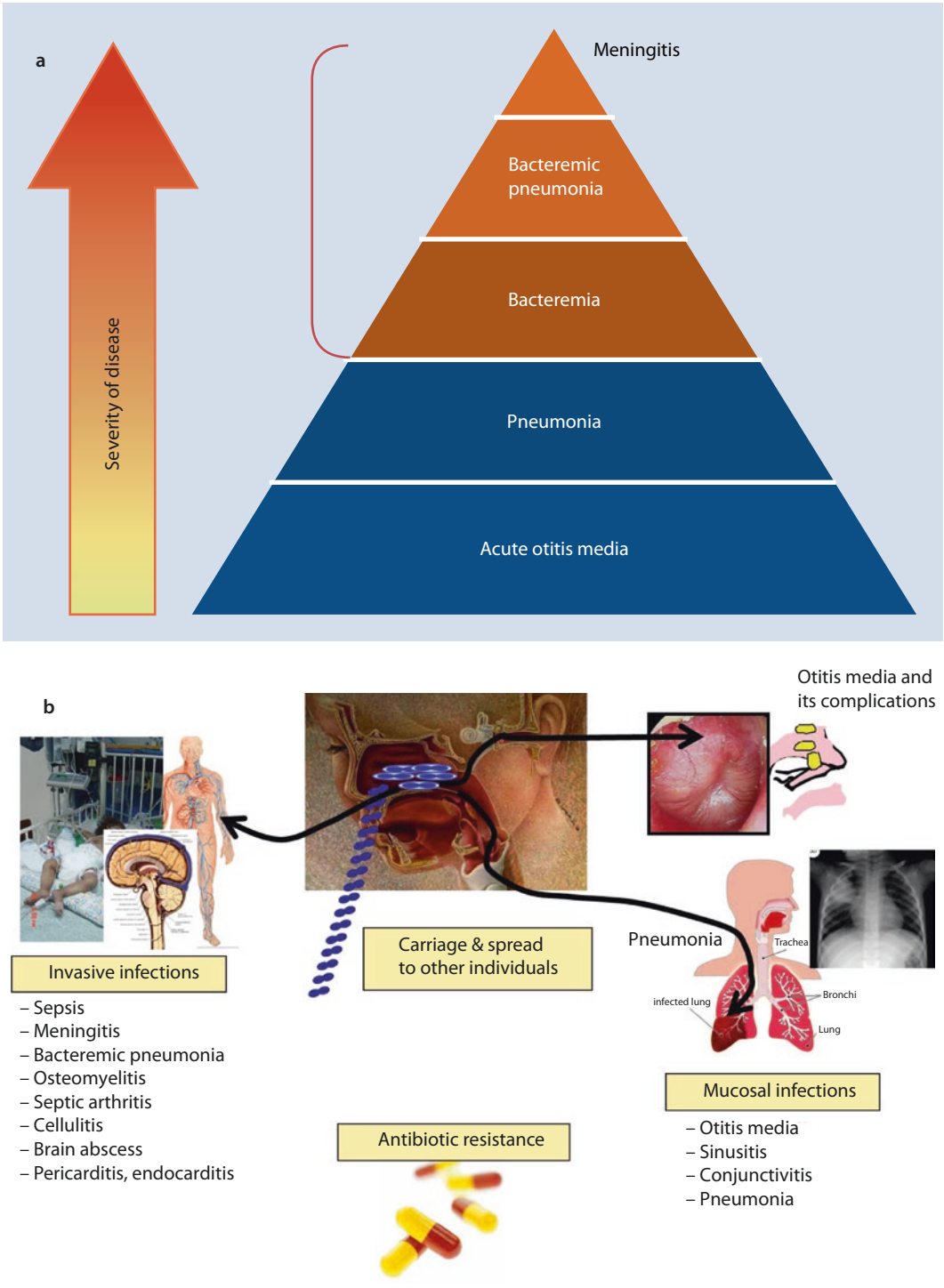


Fig. 21.2 **a** Noninvasive and IPD burden (Atkinson et al. 2009). **b** Mucosal and IPD burden

High-risk groups for the development of pneumococcal disease (both mucosal and IPD) include mostly either the very young or the elderly, children suffering from malnutrition, and immunocompromised populations (HIV, asplenia, immunosuppressive therapy, etc.).

21.2.1 IPD: Rates in the PCV era

Following PCV implementation in most European countries (see below), overall IPD rates substantially declined throughout Europe. Rates of IPD in the PCV era (for the years between 2014 and 2018) in European countries are shown in Fig. 21.3. Importantly, reported rates may reflect differences in the level of surveillance rather than true IPD rates.

21.3 *Streptococcus pneumoniae* Epidemiology

21.3.1 Pneumonia

Estimating the burden of childhood pneumonia is difficult, mainly because of the differences in case definitions and variations in trial end-points assessing this burden. The diag-

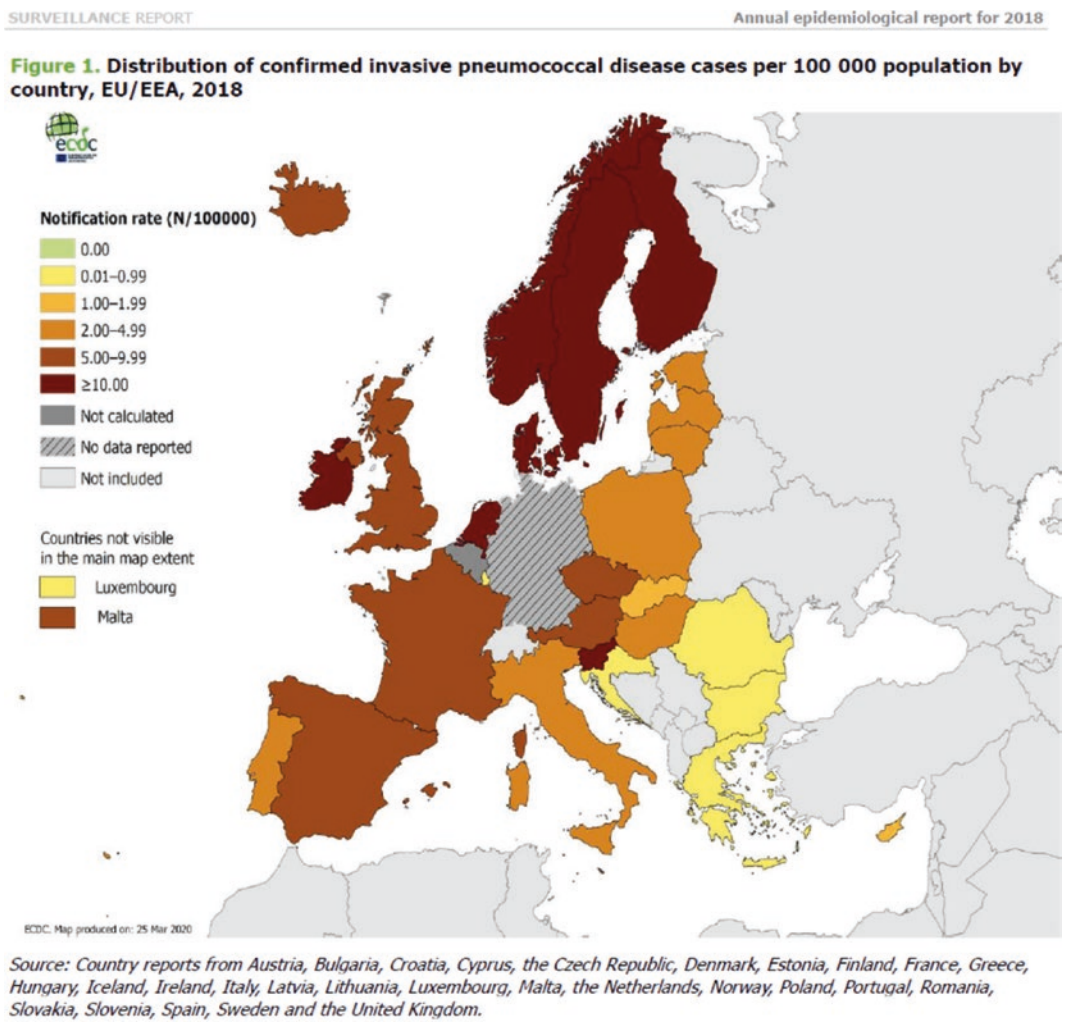


Fig. 21.3 Distribution of confirmed IPD cases and rates per 100,000 population by country, 2018

nosis of pneumonia usually derives from the clinical presentation: cough, fever, increased respiratory rate, crackles, and decreased respiration sounds. In young children, some of these clinical signs and symptoms can be absent. Radiography remains the best available tool for diagnosing pneumonia, although interobserver variations are frequent. There is usually no confirmation of etiology in pneumonia cases (except in uncommon cases of bacteremic pneumonia, mechanically ventilated children with pneumonia, and pneumonia with pleural effusion).

Pneumococcal vaccination itself offers a method of estimation of the role of pneumococci in pneumonia. Reduction in all-cause pneumonia after vaccination is likely to reflect the etiological share of pneumococci.

Although alveolar infiltrates are considered mainly compatible with bacterial pneumonia, they are not pathognomonic and are also present in viral infections or viral–bacterial co-infections (Fig. 21.4). Furthermore, the WHO guidelines for the interpretation of chest radiographs resulted in a relatively high level of agreement between readers for the definition of "alveolar pneumonia" and "no pneumonia," but poor agreement for non-alveolar pneumonia. This demonstrates the difficulties involved in reaching a consensus on the diagnosis of pneumonia.

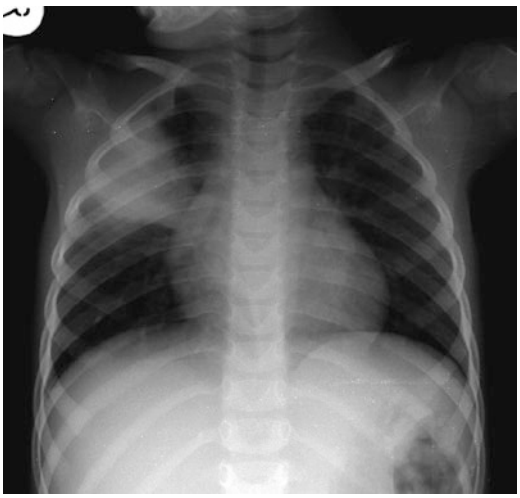


Fig. 21.4 Alveolar pneumonia on a chest X-ray

Definitive measures such as positive blood cultures are only positive in 1–10% of all alveolar pneumonia cases. Sputum cultures, routinely used in adults, have a very low yield in children, as children cannot produce deep sputum, reflecting lower respiratory tract secretions.

21.3.2 Otitis Media

Otitis media (OM) is a major public health problem in early childhood worldwide; it is estimated that most children will suffer at least once from OM, and ~20% will suffer from recurrent or chronic OM (complex OM). The OM burden is huge in terms of the number of sick children, primary physician visits, and antibiotic prescriptions. The disease peaks between the ages of 6 and 24 months. Before PCV introduction, *S. pneumoniae* accounted for approximately 30–60% of cases, and serotypes included in PCV7 and PCV13 constituted approximately 65% and 90% respectively of all pneumococcal cases. It is increasingly clear now that early OM is mainly caused by *S. pneumoniae*, especially by the more invasive serotypes, a high proportion of which are vaccine serotypes. Such early acute infections may be often missed clinically, as they may be asymptomatic or only mildly symptomatic during viral infections. Recurrent, nonresponsive, spontaneously draining, and chronic OM (termed together complex OM) are the sequelae of the first infections. In contrast to the first acute OM cases, in complex OM cases, the role of non-typeable *Haemophilus influenzae* (NTHi) is increasingly important, because, as with other chronic or recurrent respiratory tract infections, this organism recognizes damage and starts a process of prolonged infections, often involving multiple organisms and biofilm formation.

21.3.3 Mastoiditis

Acute mastoiditis is the inflammation of the mastoid process of the temporal bone that follows as a suppurative, relatively rare, com-

plication of acute otitis media. *Streptococcus pneumoniae* is regarded as one of the major bacterial pathogens causing mastoiditis.

21.4 Pneumococcal Vaccines

Two types of pneumococcal vaccines are currently available: the nonconjugated, polysaccharide vaccine (PPV23) and the 10- and 13-valent pneumococcal conjugated vaccines (PCV10 and PCV13). The conjugated vaccines (PCVs) offer several advantages over PPV23. First, PCVs are licensed for use in infants 6 weeks of age and older, whereas PPV23 is only licensed for children >2 year old. This is because PCVs already offer protection from early infancy. Second, PCVs elicit T-dependent immune response and thus also memory, which are not elicited by PPV23.

PPV23 was introduced in 1983, and is available in Europe for immunization against pneumococcal diseases caused by the 23 serotypes contained in the vaccine (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F) in adults and children aged ≥2 years.

In 2000, PCV7 (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F conjugate to CRM_{197}) was first licensed, and has increasingly been used globally. Currently, two more extended-serotype PCVs are licensed (whereas PCV7 is no longer manufactured): PCV10 (PCV7 serotypes + serotypes 1, 5, and 7F) and PCV13 (PCV10 serotypes + serotypes 3, 6A, and 19A). In PCV10, eight serotypes are conjugated to NTHi protein-D, serotype 19F to diphtheria toxoid, and serotype 18C to tetanus toxoid. In PCV13, all serotypes are conjugated to CRM_{197}.

Description of PNEUMOVAX®23™ According to SPC

► http://www.merck.com/product/usa/pi_circulars/p/pneumovax_23/pneumovax_pi.pdf

PNEUMOVAX 23 is approved for use in persons 50 years of age or older and persons aged ≥2 years who are at an increased risk for pneumococcal disease. PPV23 is not approved for use in children younger than 2 years of age because children in this age group do not develop an effective immune response to capsular types contained in the polysaccharide vaccine.

Description of Prevnar 13® According to SPC

► http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001104/WC500057247.pdf

Therapeutic indications

Active immunization for the prevention of invasive disease, pneumonia, and acute otitis media caused by *Streptococcus pneumoniae* in infants, children, and adolescents from 6 weeks to 17 years of age.

Active immunization for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in adults ≥18 years of age and the elderly.

Three-dose primary series

The recommended immunization series consists of four doses, each of 0.5 ml. The primary infant series consists of three doses, with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as 6 weeks of age. The fourth (booster) dose is recommended between 11 and 15 months of age.

Two-dose primary series

Alternatively, when Prevnar 13 is given as part of a routine infant immunization program, a series consisting of three doses, each of 0.5 ml, may be given. The first dose may be administered from the age of 2 months, with a second dose 2 months later. The third (booster) dose is recommended between 11 and 15 months of age.

Description of PHiD-CV10 (Synflorix®) According to SPC

► http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000973/WC500054346.pdf

Therapeutic indications
Active immunization against invasive disease, pneumonia, and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks up to 5 years of age.

Three-dose primary series
The recommended immunization series to ensure optimal protection consists of four doses, each of 0.5 ml. The primary infant series consists of three doses with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as 6 weeks of age. A booster (fourth) dose is recommended at least 6 months after the last priming dose and preferably between 12 and 15 months of age.

Two-dose primary series
Alternatively, when Synflorix is given as part of a routine infant immunization program, a series consisting of three doses, each of 0.5 ml may be given. The first dose may be administered from the age of 2 months, with a second dose 2 months later. A booster (third) dose is recommended at least 6 months after the last primary dose.

21.5 Pneumococcal Polysaccharide Vaccine PNEUMOVAX®23™

Pneumococcal polysaccharide vaccine (PPV23) is not included in pediatric National Immunization Programs (NIPs), as it is not approved for use in children younger than 2 years of age. It is recommended for usage in high-risk individuals ≥2 years of age, including (but not limited to) the following: asplenia (anatomical, functional), chronic renal insufficiency, cochlear implant, complement and properdin deficiency, CSF leak, hematopoietic organ disorder, HIV, hypogammaglobulinemia, immunodeficiency (congenital or acquired), malignancy, nephrotic syndrome, sickle-cell anemia, and transplantation (organ, subsequent to stem-cell transplantation). However, there is a considerable variability in vaccine recommendations among different European countries.

A second dose of PPSV23 is recommended 5 years after the first dose of PPSV23 for children who have anatomical or functional asplenia, including sickle-cell diseases, HIV infection, or other immunocompromising conditions.

Whenever PPV23 is recommended in children, it should be administered at least 8 weeks after the last PCV dose. If PPV23 was administered before PCV, administration of the latter should be delayed for at least a year.

Pneumococcal polysaccharide vaccine 23 is also recommended for adults at a high risk and all adults aged 65 years and older. The vaccine has been shown to be moderately effective in preventing invasive pneumococcal disease among the general elderly population. However, its effectiveness against IPD in the high-risk elderly may be lower. The vaccine has not been clearly demonstrated to prevent pneumonia in any age group, and it does not prevent nasopharyngeal carriage at any age.

21.6 Introduction of Pneumococcal Conjugate Vaccines and Vaccine Uptake: PCV7

Pneumococcal conjugate vaccine 7 was added to the US infant immunization schedule in 2000. In Europe, however, PCV7 introduction varied considerably among countries, with Spain, Ireland, and Luxembourg introducing PCV7, at least partially, in the years 2001 through 2003; Austria, Belgium, Italy, and Slovenia in 2004 and 2005; Greece, Slovakia, France, Netherlands, Germany, Norway, the

UK, Iceland, Malta, and Denmark in 2006 and 2007; and Poland, Cyprus, Hungary, Finland, Sweden, Czech Republic, Latvia, Bulgaria, Portugal, and Israel only during 2008 through 2010. Furthermore, vaccine uptake and recommendations regarding immunization schedule also varied considerably among countries (Table 21.2).

21.6.1 Introduction of PCV10 and PCV13

Pneumococcal conjugate vaccines 10 and 13 were introduced to most EU countries NIP (Table 21.3), with considerable variations in schedule and vaccine uptake (Table 21.4) among countries.

Table 21.2 Characteristics of national pneumococcal vaccination programs in EU countries in 2010

Country	Date PCV7 introduction	Scope of PCV7 vaccination program	Immunization schedule (dose)	Vaccine coverage[e]
Austria	July 2004	Universal	3 + 1	–
Belgium	January 2005	Universal	2 + 1	97
Bulgaria	April 2010	Universal	3 + 1/2 + 1	–
Cyprus	August 2008	Universal	3 + 1	–
Czech Republic	January 2010	Risk based	3 + 1	86.3
Denmark	October 2007	Universal	2 + 1	85
Estonia	–	–	Not decided	–
Finland	January 2009	Risk based	2 + 1	–
France	June 2006	Universal	2 + 1	81
Germany	July 2006	Universal	3 + 1	52.9
Greece	January 2006	Universal	3 + 1	–
Hungary	October 2008	Universal	2 + 1	81.1
Iceland	December 2006	Risk based	2 + 1	–
Ireland	October 2002	Universal	2 + 1	89
Israel[a]	July 2009	Universal	2 + 1	90
Italy	May 2005	Universal/risk based	2 + 1	55
Latvia	January 2010	Universal	3 + 1	51
Lithuania	–	–	3 + 1	–
Luxembourg	February 2003	Universal	3 + 1	86
Malta	January 2007	Risk based	3 + 1	–
Netherlands	June 2006	Universal	3 + 1	94
Norway	July 2006	Universal	2 + 1	90
Poland	May 2008	Risk based	3 + 1/2 + 1	1.7
Portugal	June 2010	Risk based	2 + 1	52

Table 21.2 (continued)

Country	Date PCV7 introduction	Scope of PCV7 vaccination program	Immunization schedule (dose)	Vaccine coverage[e]
Romania[b]			3 + 1	
Slovakia[c]	January 2006	Risk based	2 + 1	99.2
Slovenia	September 2005	Risk based	3 + 1	–
Spain[d]	June 2001	Risk based	3 + 1	–
Sweden	January 2009	Universal	2 + 1	–
United Kingdom	September 2006	Universal	2 + 1	90

Navarro Torné et al. (2014)
[a]Data not included in the original table
[b]PCV7 was registered in September 2007 for voluntary use on a private basis
[c]Universal as of April 2008
[d]Universal introduction in the autonomous region of Madrid in November 2006
[e]Sources: VENICE II and WHO estimates of PCV7 coverage

Table 21.3 Characteristics of national pneumococcal vaccination programs for PCV10 and PCV13 in EU countries

Country	Current vaccine introduction status	Universal introduction actual date	Current immunization program type	Current or planned formulation	Immunization schedule (dose)
Albania	Introduced into NIP	March 12, 2011	Universal	Prevnar (PCV13)	3 + 0
Andorra	Introduced into NIP	January 1, 2007	Universal	Prevnar (PCV13)	2 + 1
Austria	Introduced into NIP	January 1, 2012	Universal	Synflorix (PCV10) & Prevnar (PCV13)	2 + 1
Belarus	Introduced into NIP	N/A	Risk	Synflorix (PCV10)	3 + 1
Belgium	Introduced into NIP	January 1, 2006	Universal	Synflorix (PCV10)	2 + 1
Bosnia and Herzegovina	No decision	N/A	None	N/A	N/A
Bulgaria	Introduced into NIP	June 1, 2010	Universal	Prevnar (PCV13)	3 + 1
Croatia	No decision	N/A	None	N/A	N/A
Cyprus	Introduced into NIP	January 1, 2007	Universal	Synflorix (PCV10)	2 + 1

(continued)

Table 21.3 (continued)

Country	Current vaccine introduction status	Universal introduction actual date	Current immunization program type	Current or planned formulation	Immunization schedule (dose)
Czechia	Introduced into NIP	January 1, 2010	Universal	Prevnar (PCV13)	3 + 1
Denmark	Introduced into NIP	October 1, 2007	Universal	Prevnar (PCV13)	2 + 1
Estonia	Introduced into NIP	N/A	Risk	Synflorix (PCV10) & Prevnar (PCV13)	3 + 1
Finland	Introduced into NIP	September 1, 2010	Universal	Synflorix (PCV10)	2 + 1
France	Introduced into NIP	May 1, 2006	Universal	Prevnar (PCV13)	2 + 1
Georgia	Introduced into NIP	November 24, 2014	Universal	Synflorix (PCV10)	2 + 1
Germany	Introduced into NIP	July 1, 2006	Universal	Synflorix (PCV10) & Prevnar (PCV13)	2 + 1
Greece	Introduced into NIP	January 1, 2006	Universal	Prevnar (PCV13)	3 + 1
Hungary	Introduced into NIP	April 1, 2009	Universal	Prevnar (PCV13)	2 + 1
Iceland	Introduced into NIP	April 1, 2011	Universal	Synflorix (PCV10)	2 + 1
Ireland	Introduced into NIP	September 1, 2008	Universal	Prevnar (PCV13)	2 + 1
Italy	Introduced into NIP	May 1, 2005	Universal	Prevnar (PCV13)	2 + 1
Latvia	Introduced into NIP	January 1, 2010	Universal	Synflorix (PCV10)	2 + 1
Lithuania	Introduced into NIP	October 1, 2014	Universal	Synflorix (PCV10)	2 + 1
Luxembourg	Introduced into NIP	January 1, 2005	Universal	Prevnar (PCV13)	2 + 1
Malta	Non-Gavi planning introduction	N/A	None	N/A	N/A
Moldova, Republic of	Introduced into NIP	October 1, 2013	Universal	Prevnar (PCV13)	2 + 1
Monaco	Introduced into NIP	January 1, 2006	Universal	Prevnar (PCV13)	2 + 1
Montenegro	No decision	N/A	None	N/A	N/A

Table 21.3 (continued)

Country	Current vaccine introduction status	Universal introduction actual date	Current immunization program type	Current or planned formulation	Immunization schedule (dose)
Netherlands	Introduced into NIP	June 1, 2006	Universal	Synflorix (PCV10)	2 + 1
North Macedonia	No decision	N/A	None	N/A	N/A
Norway	Introduced into NIP	July 1, 2006	Universal	Prevnar (PCV13)	2 + 1
Poland	Introduced into NIP	January 1, 2017	Universal	Prevnar (PCV13)	2 + 1
Portugal	Introduced into NIP	July 1, 2015	Universal	Prevnar (PCV13)	2 + 1
Romania	No decision	N/A	None	N/A	N/A
Russian Federation	Introduced into NIP	March 1, 2014	Universal	Prevnar (PCV13)	2 + 1
San Marino	No decision	N/A	None	N/A	N/A
Serbia	No decision	N/A	None	N/A	N/A
Slovakia	Introduced into NIP	January 1, 2009	Universal	Synflorix (PCV10) & Prevnar (PCV13)	2 + 1
Slovenia	Introduced into NIP	January 1, 2015	Universal	Prevnar (PCV13)	2 + 1
Spain	Introduced into NIP	N/A	Regional	Prevnar (PCV13)	2 + 1
Sweden	Introduced into NIP	January 1, 2009	Universal	Synflorix (PCV10)	2 + 1
Switzerland	Introduced into NIP	January 1, 2006	Universal	Prevnar (PCV13)	2 + 1
Turkey	Introduced into NIP	November 1, 2008	Universal	Prevnar (PCV13)	3 + 1
Ukraine	No decision	N/A	None	N/A	N/A
United Kingdom of Great Britain and Northern Ireland	Introduced into NIP	September 1, 2006	Universal	Prevnar (PCV13)	1 + 1

► https://view-hub.org/data

In contrast to the late introduction of PCV7 in Europe, PCV13 and PCV10 were introduced into European countries (mostly in Western Europe) shortly after their licensure (2010 and 2011 respectively). Several countries replaced PCV7 with PCV13, including Belgium (but there was a return to PCV10 in 2015), Denmark, France, Ireland, Norway, Spain (Madrid), Switzerland, UK, Italy, and Israel.

In the Netherlands and Austria, PCV10 replaced PCV7 in 2011 and 2012, respectively,

Table 21.4 PCV10 and PCV13 vaccine uptake

Country	Year	Official country reported coverage
Albania	2019	96
Andorra	2019	96
Armenia	2019	92
Austria	2019	
Azerbaijan	2019	95
Belarus	2019	99
Belgium	2019	94
Bosnia and Herzegovina	2019	
Bulgaria	2018	89
Croatia	2019	
Cyprus	2017	81
Czechia	2019	
Denmark	2019	97
Estonia	2019	
Finland	2019	89
France	2018	92
Georgia	2019	84
Germany	2018	84
Greece	2019	96
Hungary	2019	99
Iceland	2018	90
Ireland	2019	86
Italy	2018	92
Latvia	2019	84
Lithuania	2019	79
Luxembourg	2017	95
Malta	2019	
Moldova, Republic of	2019	90
Monaco	2019	
Montenegro	2019	
Netherlands	2019	93
North Macedonia	2019	
Norway	2019	95
Poland	2018	60
Portugal	2019	98
Romania	2019	52
Russian Federation	2019	85
San Marino	2019	76
Serbia	2019	93
Slovakia	2019	97
Slovenia	2016	96
Spain	2019	95
Sweden	2019	97
Switzerland	2019	84
Turkey	2019	97
Ukraine	2016	92
United Kingdom of Great Britain and Northern Ireland	2019	91

► https://view-hub.org/data

whereas in Finland and Iceland PCV10 was introduced as the first PCV in the National Vaccination Program in September 2010 and April 2011, respectively.

Other countries, including Spain (Catalonia, Navarra), Portugal, Slovakia, the Czech Republic, and Sweden used both PCV13 and PCV10. In Germany, PCV7 was introduced to the NIP in July 2006, and was replaced by PCV10 in April 2009 and PCV13 December 2009, with PCV13 predominantly used (>90% market share). The number of European countries introducing PCV10 and PCV13 to their NIPs has been constantly increasing (Fig. 21.5).

Fig. 21.5 European pneumococcal conjugate vaccine (PCV) NIPs. *Both PCVs are available/reimbursed in the NIP or the NIP consists of difference PCVs by region PCV13 is a pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed). Czech Republic and Slovakia: Both PCVs are available and reimbursed, physicians choose which to administer to patients. Italy: PCV13 NIP in 19 out of 20 regions. Please refer to the Summary of Product Characteristics and official recommendations. 1. International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. VIEW-hub. ▶ www.view-hub.org. Accessed: 9/17/2020 2. European Centre for Disease Prevention and Control – Vaccine Scheduler. ▶ https://vaccine-schedule.ecdc.europa.eu/. Accessed: 9/17/2020 3. Data on file, Pfizer

21.7 Different Vaccine Schedules

Most schedules in European countries include two primary PCV doses in the first year of life, with a booster dose in the second year of life (2 + 1 schedule). However, several European countries have a 3 + 1 schedule, with the first three doses given in the first year of life and a booster dose at the age of 1 year or older (Fig. 21.6). Some differences also exist in the time intervals between doses and the timing of the booster.

21.8 General Comments on PCV Impact and Impact Studies

When considering the effects of a vaccine, one must understand the difference among efficacy, effectiveness, and impact. Efficacy is measuring the potential of a vaccine to protect against a specific end-point, compared with placebo or a control vaccine, in randomized control trials.

Effectiveness measures a similar effect but in real life, and is therefore affected by other factors beyond those of efficacy (i.e., refrigerator conditions, vaccination errors). Hence, effectiveness is usually assessed retrospectively and is measured by using the case–control methodology.

In contrast to efficacy and effectiveness, when measuring impact, the overall reduction (or increase) and the dynamics of rates following vaccine implementation are measured. When assessing impact, it may be more difficult to appreciate the true vaccine effect, differentiating it from potential other factors. However, these are the only studies that show the actual vaccine effect following vaccine introduction.

Several components influence the impact observed after PCV introduction. The impact of PCV on the pneumococcal carriage of vaccine serotypes (VTs) is of utmost importance. This effect is the key point in the prevention of both pneumococcal diseases among the vaccine recipients on the one hand, and the prevention

	Pneumococcal Disease: Recommended vaccinations												
	Months												
	2	3	4	5	6	10	11	12	13	14	15	18	23
Austria		PCV	PCV		PCV			PCV (1)					
Belgium	PCV		PCV					PCV					
Bulgaria	PCV		PCV					PCV (5)					
Croatia	PCV (6)		PCV (6)					PCV (6)					
Cyprus	PCV		PCV					PCV (7)					
Czech Republic		PCV (10)		PCV (10)			PCV (10)						
Denmark		PCV13		PCV13				PCV13					
Estonia													
Finland		PCV10		PCV10				PCV10					
France	PCV		PCV				PCV						
Germany	PCV		PCV				PCV				PCV (15)		
Greece	PCV13		PCV13		PCV13			PCV13					
Hungary	PCV13		PCV13					PCV13					
Iceland		PCV10		PCV10				PCV10					
Ireland	PCV				PCV				PCV				
Italy		PCV		PCV			PCV						
Latvia	PCV		PCV					PCV					
Liechtenstein	PCV13		PCV13					PCV13					
Lithuania	PCV		PCV					PCV (21)					
Luxembourg	PCV		PCV					PCV					
Malta	PCV10		PCV10					PCV10					
Netherlands		PCV		PCV			PCV						
Norway		PCV13		PCV13			PCV13						
Poland	PCV		PCV						PCV				
Portugal	PCV13		PCV13					PCV13					
Romania	PCV (25)		PCV (25)				PCV (25)						
Slovakia	PCV		PCV			PCV							
Slovenia		PCV		PCV			PCV						
Spain	PCV (28)		PCV (28)				PCV (28)						
Sweden		PCV		PCV				PCV					
United Kingdom		PCV13 (31)						PCV13					

Fig. 21.6 Recommended immunizations for pneumococcal disease in European children aged <2 years. ► http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx

Footnotes:

(1) Minimum interval of 6 months after second dose.

(2) If no previous vaccination, one dose of PPSV23 after 1 year. If previous vaccination with PPSV23, one dose of PCV13 2 years later. If previous dose of PCV13, one dose of PPSV23 2 years later.

(3) Pneumococcal vaccination is recommended in healthy adults from 65 to 85 years, in adults with comorbidity from 50 to 85 years, and in adults with an increased risk of invasive pneumococcal infection from 19 to 85 years. These target patients (comorbidity and adults with an increased risk of IPD) are specifically identified in the corresponding recommendations (► https://www.health.belgium.be/fr/avis-9210-vaccination-antipneumococcique-adultes-fiche). Vaccine schedule for complete primo-vaccination: a single dose of PCV13, followed by PPSV23 after at least 8 weeks. If vaccination in the past with PPSV23, a single dose of PCV13 at least 1 year after the last PPSV23 vaccine. Booster vaccination with PPSV23 every 5 years is recommended for adults with an increased risk of IPD. Indication for a booster vaccination for the other adult risk groups should be evaluated based on the latest evidence-based data and epidemiology.

(4) Adults over 85 years: : indication for pneumococcal vaccination should be decided on an individual basis, taking into account the individual risk of pneumococcal infection and the expected/estimated immune response to the vaccine. The vaccine schedule is the same as that recommended for the other adult target groups (► https://www.health.belgium.be/fr/avis-9210-vaccination-antipneumococcique-adultes-fiche).

(5) Not earlier than 6 months after the previous dose.

(6) Introduced in 2019.

(7) Catch-up possible until 6 years if previous recommended doses were missed.

(8) Vaccines only given on specific indications.

(9) No revaccination recommended.

(10) Recommendation only, the vaccination is covered by the health insurance.

(11) PCV for people hospitalized at long-term-illness wards and houses for seniors. Also, for at-risk groups of people based in houses for people with health disability and houses with special regime.

(12) PCV for persons from 65 years of age. Recommended only. The vaccination is covered by the health insurance.

(13) PCV 13 also recommended. For recommendations from Statens Serum Institut for vaccination of people within at-risk groups refer to ► http://www.ssi.dk/English/News/EPI-NEWS/2014/No%2040%20-%202014.aspx. There are no official recommendations from the Danish Health and Medicines Authority for use of PPV23 or PCV 13, but there is, however, reimbursement for defined at-risk groups.

(14) Recommended but not free of charge for those over 65 years. For more information on pneumococcal vaccination policy please refer to ► http://www.thl.fi/fi_FI/

web/rokottajankasikirja-fi/pneumokokkikonjugaattirokotukset.
(15) Number of doses necessary varies according to age.
(16) One dose recommended, booster doses every 6 years if indicated.
(17) PPSV is recommended in addition to PCV13 at least 2 months after the last dose of PCV13 in subjects > 2 years with an increased risk of disease from pneumococcal infections. A booster dose of PPSV23 is recommended 5 years after the first dose.
(18) One dose is recommended for all adults over age 60. For risk groups one dose of conjugated vaccine and one dose of PPS vaccine is recommended after 2 years of age. For more information see: ► https://www.landlaeknir.is/servlet/file/store93/item23265/Lei%C3%B0beiningar%20um%20notkun_b%C3%B3luefna_gegn_pneum%C3%B3kokkum-final.pdf.
(19) The vaccine is free of charge, but administration fees may be charged to patient (based on income and eligibility for free healthcare).
(20) One dose of PCV13 at 65 years and one dose PPSV after at least 8 weeks.
(21) Can be administered concomitantly with MMR.
(22) It is recommended that populations at risk and elderly 65 years of age and over receive a dose of 13-valent pneumococcal conjugate vaccine (PCV13), followed 8 weeks later by a dose of 23-valent pneumococcal polysaccharide vaccine (PCV23). In the present state of knowledge, the CSMI recommends a PPV23 recall only in people at risk, who are recalled every 5 years. Children at risk of invasive pneumococcal infection are also affected by this recommendation: In the absence of previous vaccination with PCV13, catch-up is indicated. For more information: ► http://www.sante.public.lu/fr/espace-professionnel/recommandations/conseil-maladies-infectieuses/infection-pneumocoques/index.html.
(23) Implementation starting from fall 2020. Vaccination recommended for healthy adults aged 60 to 75 years. First dose at 60 years, followed by booster doses every 5 years with a last dose at 75 years. More information available at: ► https://www.rivm.nl/pneumokokken/pneumokokkenvaccinatie-voor-ouderen.
(24) One dose if not vaccinated in the previous 10 years. Reimbursed for some at-risk groups.
(25) Pneumococcal conjugate vaccine will be included in the national vaccination calendar depending on available funds.
(26) Recommended to all. Mandatory to persons residing in social care facilities.
(27) PCV and PPSV23 recommended, self-paid.
(28) For recommendations in children and adults with high risk-conditions. Please refer to ► https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/VacGruposRiesgo/docs/VacGruposRiesgo_todas_las_edades.pdf.
(29) For recommendations in children and adults with high risk conditions, refer to: ► https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/VacGruposRiesgo/docs/VacGruposRiesgo_todas_las_edades.pdf.
(30) Funding varies by region.
(31) Recommended at 12 weeks.

of spread and early exposure to vaccine-type strains in unvaccinated individuals on the other hand, resulting in indirect (herd) protection. Other important components determining PCV impact include vaccine uptake (affecting both direct and indirect impact), serotype coverage of the vaccine (PCV7, -10, -13), time elapsed since vaccine introduction (affecting the indirect impact), vaccine efficacy against different disease end points (i.e., IPD vs. mucosal), and local epidemiological characteristics, including serotype distribution before PCV introduction and immunodeficient population (i.e., HIV prevalence).

Impact studies are also important in advancing our understanding of the role of vaccine-type pneumococcal serotype in the etiology of mucosal syndromes, such as pneumonia and OM. In the case of OM, the introduction of PCV7 resulted in a moderate effect of up to ~25% reduction in OM rates. Further studies conducted following PCV13 introduction observed substantial (up to ~70%) reduction of overall OM, with the near elimination of vaccine-type OM, mainly complex OM. These findings hint at a new paradigm, suggesting that early OM episodes might mainly be caused by PCV13 serotypes, and that preventing these episodes might result in preventing acute OM sequelae, including complex OM. Similarly, the introduction of PCV13 resulted in a substantial reduction of pneumonia episodes, to the magnitude of 50%, suggesting the major role of vaccine serotypes in the etiology of pneumonia. Thus, impact figures, depending on multiple factors and endpoints acting in concert, are much greater than those calculated for efficacy. The observations with regard to PCV impact on disease, elucidating the role of vaccine-type strains in disease etiology are termed "vaccine probe" studies.

21.9 Implementation of PCV and Post-PCV Impact

True appreciation of the impact of a vaccine depends on a reliable, long-standing, pre-vaccine surveillance system. In this regard, there is a real gap of knowledge, as for the pre-PCV pneumococcal disease rates, especially beyond IPD. Although IPD rates are relatively easy to estimate, this is not the case with pneumonia and OM, as disease rates are highly variable because of differences in case definitions and the lack of national surveillance systems in most countries.

In general, all PCVs lead to a rapid and profound reduction in pneumococcal disease rates in vaccinated infants and children if widely introduced, and most studies also showed an indirect effect (herd protection) in older individuals who were not vaccinated.

The first seven-valent pneumococcal conjugated vaccine (PCV7) was developed based on data demonstrating that within the USA and several other developed countries, the PCV7 serotypes were responsible for >80% of IPD in young children. Subsequent studies showed the important global role of additional serotypes, especially 1, 3, 5, 7F, 6A, and 19A. For one vaccine (PCV10, also termed PHiD-CV), efforts were made to add serotypes 1, 3, 5, and 7F to form an 11-valent vaccine, but following the failure to demonstrate protection against serotype 3 in an otitis media efficacy study, the final product has added only three additional serotypes (1, 5, and 7F) to the initial seven.

For the formulation of both PCV7 and PCV10, it was assumed that serotypes 6B and 19F present in these vaccines could protect against the prevalent and important (including often antibiotic-resistant) serotypes 6A and 19A, respectively. For serotype 6A, cross-protection by serotype 6B was seen, at least for IPD, in fully vaccinated children. For 19A, no cross-protection was shown using PCV7. Limited cross-protection was observed for 19A in fully vaccinated infants with PCV10. However, probably because of the short duration of protection against IPD and the absence of efficacy against carriage, the overall picture post-implementation in the community regarding serotype19A resembled that of PCV7, with an overall increase in disease in all ages in most countries using PCV10, which have been conducting appropriate epidemiological surveys. The prolonged use of PCV7 in some countries resulted in reduced disease caused by serotype 6A in all ages. Similarly, in countries using PCV10, a reduction in serotype 6A IPD in children aged <5 is usually observed. However, beyond this age group, the effect is dependent upon indirect protection derived from the impact on carriage, and thus has been more variable. In most countries using PCV10, rates of serotype 6A IPD in adults either did not decrease or even increase, meaning that the impact of PCV10 on 6A carriage in vaccine recipients was often insufficient.

Pneumococcal conjugate vaccine 13 was licensed in 2010. Implementation of this vaccine in several countries with well-conducted epidemiological studies and high vaccination coverage has shown a rapid reduction of the additional serotypes in all ages and for all endpoints. The one exception is serotype 3, where contradictory data were generated regarding its impact after the first 5–6 years post-PCV13 implementation. The final verdict concerning its impact on serotype 3 disease has not yet been reached.

In contrast to PCV7 and PCV10, the introduction of PCV13 resulted in a rapid and profound decrease in all endpoints of disease and carriage by serotypes 6A and 19A in all ages. Furthermore, the presence of serotype 6A antigen in PCV13 resulted in its impact on disease from the carriage of cross-reactive serotype 6C, one of the most important replacing serotypes after the implementation of PCV7 or PCV10.

21.10 PCV Schedules

Post-implementation, the impact of the two different schedules were not directly compared, except in a double-blind, randomized controlled Finnish trial designed to document the effectiveness of the PCV10 vaccine against

invasive pneumococcal disease, where vaccine effectiveness estimates of both 3 + 1 and 2 + 1 schedules were similar. However, the differences between the two regimens could not be fully assessed for all outcomes because of the paucity of outcome cases. Furthermore, whether data for comparison by one vaccine (PCV10) can directly be extrapolated to another vaccine (PCV13) is not clear.

Some data exist, though, to compare the impact of the various regimens on carriage. In VT carriage, antibody concentrations post-PCV administration may be related to efficacy. Thus, efficacy against carriage after two infant doses may be reduced compared with after three doses. PCV10 studies in Finland suggested that for PCV10, even after a booster, the 2 + 1 regimen is inferior to the 3 + 1 regimen.

In any case, even in countries with a 2 + 1 regimen, it is recommended that immunodeficient individuals (including those born prematurely) receive an additional PCV dose (i.e., a 3 + 1 schedule).

In the UK, a 1 + 1 regimen is used since 2018, replacing a 2 + 1 regimen.

Joint Committee on Vaccination and Immunisation. Minutes of the meeting on 06 June 2018. Available at: ► app.box.com/s/iddfb-4ppwkmtjusir2tc/file/305779572165 ► www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation#minutes

21.11 Impact of PCV on IPD in Young Children

Although IPD constitutes only a small proportion of all pneumococcal diseases, it is extremely important, as some of the IPD manifestations (i.e., sepsis, meningitis) are the most severe pneumococcal disease manifestations and result in the highest mortality rates.

The introduction of PCV7, PCV10, and PCV13 was associated with a rapid and profound reaction in IPD caused by the respective vaccine serotypes in children <5 years old. In countries introducing first PCV7, its replacement by PCV10 or PCV13 further reduced IPD caused by the additional serotypes, showing a two-step reduction pattern (◘ Fig. 21.7). As discussed above, for the cross-reacting serotype 6A, all three PCVs showed a similar impact in young children. However, no apparent impact on serotype 19A was observed in countries using PCV10 and in several countries (i.e., Finland, Chile, and New Zealand), IPD caused by serotype 19A even increased in young children. IPD caused by some non-VTs increased in young children after the introduction of PCV, the most commonly observed serotypes in countries using PCV10 or PCV13 being 8, 12F, 15A, 15B/C, 22F, 24F, and 33F. In addition, following the introduction of PCV10, disease caused by serotype 3 also frequently increased.

As most of the non-PCV serotypes are less invasive than most PCV serotypes, it is not surprising that post-PCV implementation, the proportions of compromised patients increased within cases of IPD.

In France, as well as in other countries, PCV13 implementation led to a major reduction in the incidence of IPD. However, a rebound in cases among children and adults since 2015, driven by several emerging non-PCV13 serotypes, jeopardizes the long-term PCV benefits.

In general, the overall impact of PCV7/PCV13 in children was less prominent in meningitis than in non-meningitis IPD, probably attributable to the younger age of children with meningitis and some underlying conditions resulting in differences in causative serotypes between the two groups, as the decline of VT meningitis and non-meningitis IPD was similar.

21.12 Impact of PCV on Pneumonia

Estimating the impact of PCV on pneumonia rates is difficult, for two main reasons: (1) the definition of pneumonia is not clear, as will be discussed later; and (2) the microbiological diagnosis of pneumonia is complex and unclear. As expected, the highest reductions were observed in studies evaluating bacteremic pneumococcal pneumonia (accounts for ~25–35% of all IPD cases), where disease

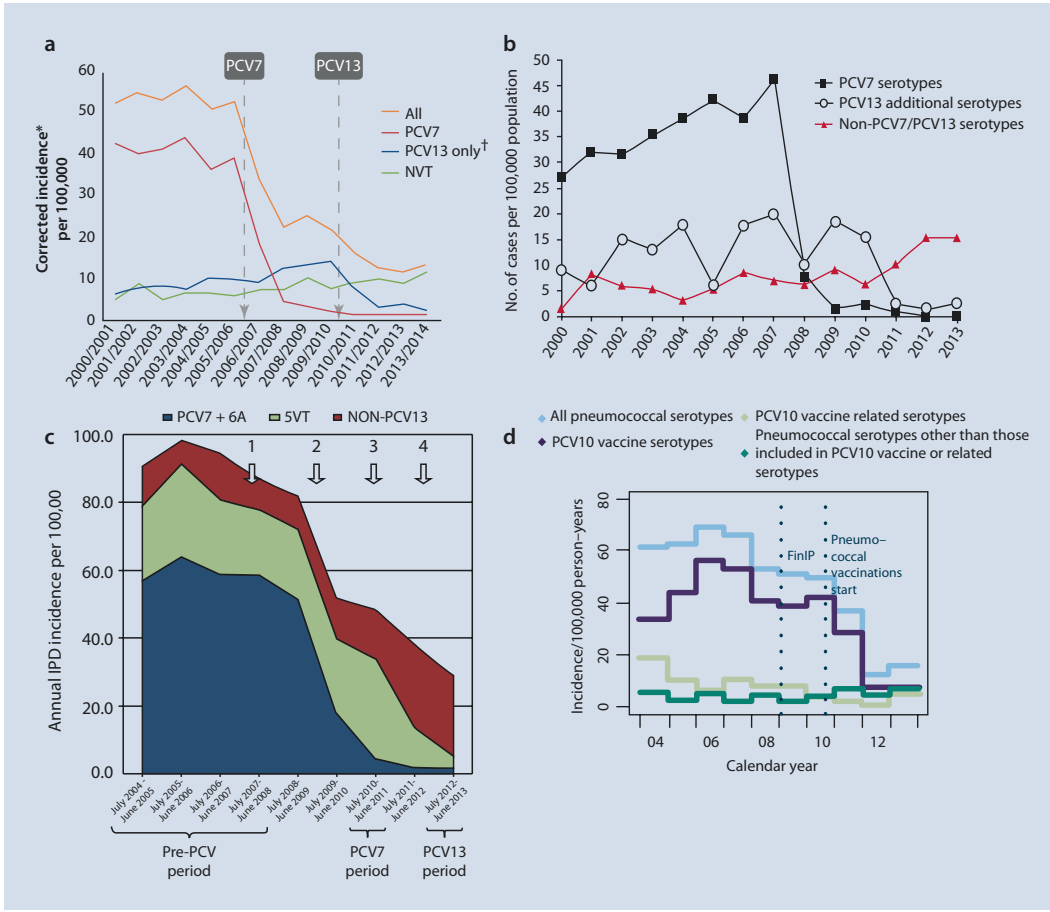


Fig. 21.7 Incidence of IPD in children <2 years before and after PCV introduction in England and Wales, Denmark, Israel, and Finland. **a** England and Wales, PCV13; **b** Denmark, PCV13; **c** Israel, PCV13; **d** Finland, PCV10

rates declined in a similar manner to those of other non-pneumonia IPD.

Microbiological studies in cases of empyema or pleural effusion (pleuropneumonia) suggest that the most common serotypes, accounting for >50% of cases, might be serotype 14 (a PCV7 serotype) and the additional PCV10/PCV13 serotypes 1, 3, 5, 7F, and 19A. Thus, it is not surprising that post PCV7 implementation, pleural pneumonia did not decrease and even increased. However, post-PCV10 and PCV13 implementation, the incidence declined. As pleuropneumonia and bacteremic pneumonia constitute only a minority of pneumonia cases, in most other pneumonia cases, only partial information on the causative serotype exists.

When alveolar pneumonia (also termed lobar or segmental pneumonia) was examined, post-implementation reduction of up to 50% or more was seen, especially after PCV10 and PCV13 implementation (emphasizing the importance of serotype 1, 5, 7F, and 19A in pneumonia). This type of pneumonia is usually considered to be of bacterial origin, mainly pneumococcal.

These observations are consistent with the finding that the highest efficacy against pneumonia in randomized clinical studies with PCV7 and PCV10 was observed for alveolar pneumonia. However, much more common, but less obviously of pneumococcal origin, were all-cause pneumonia cases (a term that includes all end-points of pneumonia, such

as non-alveolar, chest radiology-negative pneumonia, or even clinical-only pneumonia). For these more inclusive but less-specifically defined cases, overall reduction, as expected, was more variable, ranging from <20% to ~70%. In any case, the repeated findings of reduced rates of all-cause pneumonia emphasize not only the pneumococcal role in pneumonia, but probably the important role of vaccine serotypes as causative agents in all-cause pneumonia. These "vaccine probe" studies, in fact, showed clearly that the impact on pneumonia was much greater than initially expected, with the number of prevented cases higher by orders of magnitude than the IPD figures.

21.13 PCV Impact on Otitis Media

Pre-licensure efficacy studies showed an efficacy of 57–67% against PCV7 serotype OM. PCV7 also showed a similar reduction for the cross-reacting serotype 6A. In contrast, rates of OM caused by non-PCV7 serotype did not decrease in these efficacy studies and in some cases even increased, along with nonpneumococcal cases. This resulted in an only modest efficacy against all-cause OM that did not reach statistical significance in most studies. However, measuring the overall OM incidence does not appropriately reflect the real OM burden, which is better reflected by measuring the impact of OM sequelae, such as recurrent, nonresponsive, and chronic OM (collectively termed complex OM). Although *S. pneumoniae* is not the only major pathogen in OM, it is found mostly in early OM, and becomes less prominent later, when the frequency of complex otitis increases. In complex OM, a high frequency of NTHi is observed, sometimes with *Moraxella catarhallis* and other organisms, and frequent findings of biofilm formation. Thus, it is plausible that preventing early, acute pneumococcal OM might reduce the burden imposed by its sequelae. Indeed, pre-PCV7 licensure randomized controlled studies and post-introduction impact studies showed a significant reduction in OM-associated burden due to complex OM, with a reduction of recurrent otitis or ventilation tube insertions, despite the paucity of the presence of VT pneumococci at these end points. Despite the increasing evidence for such an impact, the lack of post-PCV microbiological data raised some skepticism regarding the actual extent of OM burden reduction by PCVs. This was mainly because measuring pathogen-specific impact is particularly problematic, as it depends on obtaining middle-ear fluid cultures, usually performed selectively.

In Israel, the impact of PCV13 on OM cases necessitating middle-ear fluid cultures (mainly complex OM cases) was documented in a population-based, active surveillance system in children <3 years old. Following the sequential introduction of PCV7/PCV13, a decline of 95% in the incidence for the PCV7 + 6A serotypes was observed with a decline of 89% in the incidence of the additional PCV13 serotypes (1, 3, 5, 7F, and 19A) disease. Overall, complex OM-enriched pneumococcal OM incidence declined by 78%. Furthermore, non-pneumococcal OM episodes were also reduced, as expected. In this regard, it is important to remember that it has been long recognized that early OM cases in young infants are most likely to be associated with complex OM cases in large studies.

The prevention of early OM post-PCV implementation is an excellent example of dual protection provided by PCV. On the one hand, it reduces VT carriage (see in later paragraphs) to an extent where very young infants rarely encounter any VT in the community, and on the other hand, once the infants encounter one of the VTs, the vaccine provides additional direct protection against disease. Thus, the prevention of early encounters with vaccine-type *S. pneumoniae* results in a marked reduction of early acute OM episodes, and therefore, the subsequent sequelae.

With regard to PCV10, one hoped to see a direct effect of the vaccine on NTHi OM, as most serotypes in PCV10 (or its precursor PCV11) are conjugated to NTHi-derived protein-D. However, even though protein-

D was immunogenic, PCV10 did not show direct protection against any NTHi outcome. One study suggested an exception. The POET study was conducted in the Czech Republic and Slovakia using PCV11 (the precursor of PCV10) against OM. This placebo-controlled study showed a significant reduction against NTHi-OM. However, in this study, the trigger to enroll children was for children visiting an otolaryngologist office, thus enriching the population with complex cases. Thus, the reduction of NTHi OM by protein-D conjugated PCV, documented only in the POET study, could be explained again by the prevention of early pneumococcal OM with a secondary prevention of NTHi otitis as part of the sequelae.

Another study on the efficacy of PCV10 against OM (the COMPAS study), conducted in Latin America, failed to show any effect of PCV10 on NTHi OM.

Post-PCV10 impact data on OM are scarce, but recent data from Iceland and Brazil suggest trends toward reductions of OM and recurrent OM. However, whether the extent of the impact will be similar for the PCV10 and PCV13 remains to be clarified.

21.14 PCV Impact on Carriage and the Resulting Indirect (Herd) Protection

The widespread introduction of PCV7 resulted in a rapid and substantial indirect (herd) protection. Herd protection is achieved through a reduction in the carriage of vaccine serotype pneumococci in vaccinated children, and thus a reduction of their spread in the community. On the other hand, the near elimination of the NP carriage of VT following PCV introduction led to replacement of the carriage by non-VTs, often less invasive. Because non-VT strains were less invasiveness overall, partial or no replacement disease was observed in most studies. Therefore, the disease replacement phenomenon was limited and was mainly observed in compromised patients. As elderly people can often be considered immunocompromised, it is not surprising that this population was most affected by the increase in non-VT strains in the community, following PCV introduction. However, a longer follow-up is needed to ascertain the continuous net-positive effect of PCVs regarding replacement disease.

As all PCVs reduce the nasopharyngeal carriage of VT pneumococci, widespread vaccination resulted in reduced circulation of these serotypes in the community, hence the reduced encounters of both vaccinated and unvaccinated individuals with vaccine serotypes. As discussed above, the reduction in nasopharyngeal carriage is the most important factor determining impact, along with vaccination coverage. The reduced carriage protects both vaccinated and unvaccinated individuals. As an example, if PCVs have ~60% efficacy against VT OM, and if at the same time there is a 60% reduction in VT carriage, the vaccinated infants encounter only 40% of what he or she would have encountered in the pre-PCV era. In this given example, the dual protection results in ~85% protection against VT pneumococcal OM.

Three main groups that have herd protection:

1. Those who are too young to be vaccinated (i.e., infants aged <4 months who usually by this age have only ≤1 doses); this early protection against VT disease may be the most important means of preventing complex OM, as very early OM (before reaching the age of full vaccination) is the most important risk factor for complex OM (beyond genetics).
2. The vaccinated individual (as specified above), as efficacy never reaches 100%.
3. Individuals too old to be vaccinated (practically all individuals >5 years of age).

We do not know how long the immunity afforded by PCVs lasts, especially in terms of mucosal immunity, but the indirect protection also ensures that those immunized in the past can be protected, even if they had already lost the vaccine-acquired immunity.

As discussed previously in this chapter, not all PCVs are equally efficacious against carriage in general, and some possess unique serotypes that others do not have. However,

in general, in all countries where PCVs were introduced, an impressive reduction of IPD caused by vaccine-serotype pneumococci was recorded at all ages, because of the combined direct and herd protection. However, in compromised patients (including the elderly), replacement diseases caused by non-VTs is common. Current epidemiology data strongly suggest that PCV13 might provide a more rapid and profound herd protection, especially because of the reduction of the carriage of serotypes 6A, 19A, and the cross-reacting serotype 6C, compared with PCV10. A longer period of follow-up is needed to confirm these findings.

21.15 PCV Impact on Antibiotic Resistance

In the field of pneumococci, the general term for antibiotic nonsusceptibility is often preferred over the term "resistance," as at times, especially for β-lactams antibiotics, the minimal inhibitory concentration (MIC) increases, meaning that the organism is less susceptible to the drug, but no full resistance has yet been reached. It is well established that antibiotic nonsusceptibility among pneumococci (like most bacteria) can rarely occur by mutation, but rather widespread antibiotic use is the main contributor to the promotion of carriage and the circulation of antibiotic-nonsusceptible *S. pneumoniae* (ANSP) . The main antibiotics responsible for ANSP promotion and spread are the long-acting macrolides (in particular, azithromycin) and oral cephalosporins, whereas the least powerful promoter is high-dose amoxicillin (with or without clavulanate). However, any antibiotic drug can promote ANSP, and thus indiscriminate use of antibiotics, which has often been practiced since the 1980s in many societies, is responsible for increasing ANSP prevalence. Since ANSP resides in the nasopharynx, antibiotic drugs given for any reason, will select these strains over susceptible ones, resulting in their promotion and spread in the community.

Among pneumococci, the most successful colonizers in young children are serotypes 6A, 6B, 9V, 14, 19A, 19F and 23F. These serotypes are also the main strains that express multidrug resistance and high-level resistance. They are also responsible for most disease (both IPD and mucosal diseases) in children and adults. Therefore, it is not surprising that the most important ANSP serotypes are included in the vaccines. Of these, serotypes 6B, 9V, 14, 19F, and 23F are included in PCV7, which also confers some cross-protection against serotype 6A (although as reviewed above, not complete in the case of carriage). PCV10, which adds the important serotypes 1, 5, and 7F beyond PCV7, does not significantly improve the impact on ANSP prevalence, as these three additional serotypes are rarely carried and rarely nonsusceptible. However, the addition of serotypes 6A and 19A in PCV13 made an important contribution, as these two serotypes are often multidrug-resistant with a high level of resistance. This is the basis for the potential reduction of ANSP disease and circulation by PCVs.

All PCVs were shown to reduce antibiotic nonsusceptibility by three main mechanisms. First, they reduce VT disease (efficacy against pneumococcal diseases), including disease caused by the VT ANSP; second, they reduce the carriage and thus the spread of ANSP; third, the reduction of disease incidence results in a reduction of antibiotic use and thus a reduction in the antibiotic pressure on strains carried in the nasopharynx or other sites of the flora microbiota. These positive forces by the vaccine, are necessarily accompanied by a marked (although many times not complete) replacement in the carriage by non-VT. Nonsusceptibility, especially high-level and multidrug resistance, was remarkably less common among non-VTs before the introduction of PCVs. However, post-vaccination, by occupying the nasopharynx more frequently and for longer periods because of replacement, the non-VTs are now under increased antibiotic pressure. Indeed, ANSP and even multidrug resistance among non-VTs are increasing at an alarming rate. However, because in general the overall invasiveness among non-VTs is lower compared with VTs (with a few exceptions, i.e., serotypes 12F, 24F, 8, and 22F), the net effect is usually reduced

disease caused by ANSP. It is not surprising that in adults, ANSP disease is influenced by childhood widespread PCV vaccination, through the major change in nasopharyngeal carriage. Thus, in many respects, ANSP IPD in adults follows that of childhood.

As discussed before, several serotypes (i.e., serotypes 8, 10A, 11A, 12F, 15A, 15B/C, 22F, 33F, and 35B) are generally the most important replacing serotypes, meaning that most of these are successful colonizers in the absence of competition with VTs. Therefore, it is only natural that increasing resistance and multidrug resistance are found in some of these serotypes. This scheme is especially worrisome in compromised patients, in whom replacement disease is most frequent.

21.16 Future Vaccines

All currently licensed pneumococcal vaccines have limitations due to their capsular serotype specificity.

Potential approaches to addressing current PCV limitations include higher valency PCVs. Efforts to develop extended spectrum (higher valency) PCVs have led to the development of 15- and 20-valent PCVs (PCV15, PCV20), both currently in advance stages of clinical studies. The experimental PCV20 includes, beyond the 13 serotypes of PCV13, the additional pneumococcal serotypes 8, 10A, 11A, 12F, 15B/C, 22F, and 33F, two of which (serotypes 22F and 33F) are also contained in PCV15. These additional PCV20 serotypes (VT20-13) have been increasingly observed in recent years as being common IPD serotypes.

One alternative possibility is to have additional PCVs with some of the common replacement serotypes to be administered sequentially after PCV10/PCV13, or to adults only. Another alternative is to use pure protein of *S. pneumoniae* or polypeptide derivatives to develop protein-based vaccines. Protein vaccine candidates are ideally highly conserved by all pneumococcal strains, and exhibit high immunogenicity. However, so far, all attempts to develop such vaccines were not successful. Thus, it seems that in the next 5–10 years, no protein vaccine will emerge and be licensed for general use. A further possible approach is the use of whole killed cell vaccines, currently in human trials.

Bibliography

Atkinson W, et al., Epidemiology and prevention of vaccine-preventable diseases. CDC Pink Book. 11th Washington DC: Public Health Foundation; 2009. p. 217–30.

Ben-Shimol S, Givon-Lavi N, Leibovitz E, Raiz S, Greenberg D, Dagan R. Near-elimination of otitis media caused by 13-valent pneumococcal conjugate vaccine (PCV) serotypes in southern Israel shortly after sequential introduction of 7-valent/13-valent PCV. Clin Infect Dis 2014;59(12):1724–32.

Dagan R. Impact of pneumococcal conjugate vaccine on infections caused by antibiotic-resistant *Streptococcus pneumoniae*. Clin Microbiol Infect 2009;15(Suppl 3):16–20.

Isaacman DJ, McIntosh ED, Reinert RR. Burden of invasive pneumococcal disease and serotype distribution among *Streptococcus pneumoniae* isolates in young children in Europe: impact of the 7-valent pneumococcal conjugate vaccine and considerations for future conjugate vaccines. Int J Infect Dis 2010;14(3):e197–209.

Navarro Torné A, et al. European enhanced surveillance of invasive pneumococcal disease in 2010: data from 26 European countries in the post-heptavalent conjugate vaccine era. Vaccine 2014;32(29):3644–50.

Nuorti JP, Whitney CG, Centers for Disease Control and Prevention (CDC). Prevention of pneumococcal disease among infants and children – use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine – recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2010;59(RR-11):1–18. http://ecdc.europa.eu/en/publications/Publications/0701_TER_Use_of_pneumococcal_polysaccharide_vaccine.pdf

O'Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. Lancet 2009;374:893–902.

Palmu AA, Jokinen J, Borys D, Nieminen H, Ruokokoski E, Siira L, et al. Effectiveness of the ten-valent pneumococcal Haemophilus influenzae protein D conjugate vaccine (PHiD-CV10) against invasive pneumococcal disease: a cluster randomised trial. Lancet 2013;381(9862):214–22. Lancet Infect Dis. 2020:S1473-3099(20)30165-1. doi: 10.1016/S1473-3099(20)30165-1

Ben-Shimol S, Dagan R, Givon-Lavi N, Avital D, Bar-Ziv J, Greenberg D. Clin Infect Dis 2020a;71(1):177–187. doi: https://doi.org/10.1093/cid/ciz768.

Ben-Shimol S, Givon-Lavi N, Greenberg D, van der Beek BA, Leibovitz E, Dagan R. J Antimicrob Chemother 2020b;75(10):3038–3045. doi: https://doi.org/10.1093/jac/dkaa263.

Thompson A, Lamberth E, Severs J, Scully I, Tarabar S, Ginis J, et al. Phase 1 trial of a 20-valent pneumococcal conjugate vaccine in healthy adults. Vaccine 2019;37:6201–7.

Rupp R, Hurley D, Grayson S, Li J, Nolan K, McFetridge RD, et al. A dose ranging study of 2 different formulations of 15-valent pneumococcal conjugate vaccine (PCV15) in healthy infants. Hum Vaccin Immunother 2019;15:549–59.

Meningococcal Vaccines

Andrew J. Pollard, Matthew D. Snape, and Manish Sadarangani

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_22

22.1 Introduction

Meningococcal disease was first described in Europe as a characteristic outbreak in Geneva in 1805. *Neisseria meningitidis* (the meningococcus) is a Gram-negative diplococcus, divided into capsular groups determined by the polysaccharide capsule. Six of the twelve groups (A, B, C, W, X and Y) are responsible for almost all invasive disease worldwide. While asymptomatic nasopharyngeal infection (colonisation or carriage) occurs in approximately 10% of the population, bacteria occasionally enter the bloodstream to cause devastating invasive diseases such as meningitis and septicaemia. In Europe, it is typically a rare endemic disease, but hyperendemic and epidemic disease patterns also occur. Disease onset may be rapid and has a high case fatality rate, especially in those with septic shock. Many survivors suffer long-term neurological and non-neurological sequelae. Prevention of disease through vaccination is the only realistic prospect for disease control.

22.2 The Clinical Spectrum of Meningococcal Disease

Meningococcal infection ranges from asymptomatic nasopharyngeal carriage to fulminant septic shock, which can cause death within a few hours. Septicaemia and acute meningitis are the commonest manifestations of invasive disease. Meningococcal sepsis is classically described as a syndrome of fever and widespread purpura, with or without shock. Occult bacteraemia and chronic meningococcaemia can also occur. Occasionally the disease manifests as a focal infection such as pneumonia, septic arthritis, osteomyelitis, myocarditis, pericarditis, peritonitis, conjunctivitis, endophthalmitis, sinusitis or otitis media.

Invasive disease often rapidly progresses from a non-specific febrile illness, indistinguishable from minor viral infections, to fulminant septicaemia and/or severe meningitis. In children who ultimately develop septicaemia, fever, nausea and vomiting, and lethargy are the most frequent early symptoms. A blanching, salmon-coloured, maculopapular rash, similar to viral exanthems, may also be present. As disease progresses, signs of shock become more apparent. A rash occurs in 70–80% of meningococcal bacteraemia cases at hospital presentation and is usually non-blanching (i.e. petechial or purpuric). Most affected patients have only non-specific symptoms in the first 4–6 h of symptom onset, with the petechial/haemorrhagic rash, meningism and impaired consciousness developing later at a median of 13–22 h. Meningitis has more non-specific clinical features in infants and young children, when disease incidence is highest, compared with older children. Initial symptoms usually include fever, nausea and vomiting, photophobia and severe headache. Seizures can occur early or later in disease. Irritability, delirium and altered level of consciousness develop as central nervous system (CNS) inflammation progresses. The most specific signs are neck stiffness, associated with Kernig and Brudziński signs, but these are often absent in children. Focal neurological abnormalities and signs of raised intracranial pressure may also occur. Where septicaemia and meningitis coexist, neurological features are due to cerebral ischaemia and/or meningeal inflammation.

Despite medical advances, the case fatality rate in industrialised countries has remained around 5–15% since the 1950s, although some specialist centres have reported a case fatality rate of 5% with early aggressive circulatory support. Early neurological complications include seizures, syndrome of inappropriate antidiuretic hormone (SIADH), subdural effusions and empyema, hydrocephalus, raised intracranial pressure, focal neurological abnormalities, venous sinus thrombosis and cerebral infarction. Sequelae secondary to severe shock occur due to tissue hypoperfusion and include skin necrosis and subsequent scarring (which may need skin grafting) and gangrene of parts or entire limbs, requiring amputation. Growth plate damage may require multiple surgical procedures until growth is complete. There are very high rates of significant sequelae in survivors (up to 20–30% in most studies), leading to long-term disability. These include sensorineural hearing

loss, epilepsy, learning difficulties, and motor/cognitive impairment. Arthritis can lead to permanent joint damage. Studies of longer-term outcomes, up to 15 years, after disease have described sequelae in up to 50–60%, including physical and neuropsychiatric problems. Significant emotional problems in close family members have also been found, highlighting the societal impact.

22.3 Epidemiology of Meningococcal Disease in Europe

Invasive meningococcal disease is rare in Europe, with annual overall rates of 0.5–0.7 cases per 100,000 population and variation between 0.1 and 3.0 cases per 100,000 population, depending on the country, between 2013 and 2017. Highest rates occur in Lithuania, Ireland, the Netherlands, Croatia and the United Kingdom. Infants (under 1 year of age) have the highest disease incidence rates (8.2 per 100,000 per year), followed by 1–4-year-olds and adolescents/young adults aged 15–24 years. Most cases in 2017 were caused by group B organisms (51%), followed by group W (17%), C (16%) and Y (12%). Between 2013 and 2017, disease caused by group B organisms decreased, partly due to introduction of a recombinant protein vaccine including outer membrane vesicles targeting group B organisms in several countries, comprising the UK (in 2015), followed by Austria, Greece, Ireland, Italy, Lithuania and Malta (Fig. 22.1a, b). In contrast, there has been a steady increase in group W cases across Europe, due to clonal expansion following introduction of a clonal complex group W strain in the UK in 2009–10. This strain is distinct from the 2000 Hajj-associated outbreak of meningococcal capsular group W (MenW), which spread worldwide and lasted for several years. In 2017, MenW was responsible for 17% of all cases of invasive disease, compared with historical levels of 1–2%. Overall there has been an approximately threefold increase of group W between 2013 and 2017, from 0.03 to 0.10 cases per 100,000 per year (Fig. 22.1a, b). This increase has been most pronounced among young children and adults above 50 years of age. This increase prompted the change in the UK adolescent booster from the monovalent meningococcal capsular group C (MenC) vaccine to quadrivalent meningococcal A, C, W and Y (MenACWY) vaccine in September 2015. In Austria, Ireland, Italy, Spain and the United Kingdom, an adolescent booster of the quadrivalent MenACWY conjugate vaccine following the conjugate MenC vaccine in younger children is used, and in the Czech Republic, Greece, Malta, the Netherlands and Switzerland the quadrivalent vaccine is used for all doses (Fig. 22.2).

22.4 Polysaccharide Vaccines

The first meningococcal vaccines in regular use were plain polysaccharide vaccines developed in the 1960s. These vaccines are based on the capsule which surrounds the organism and is used for grouping and were produced to target disease caused by groups A, C, W and Y with bivalent MenAC and quadrivalent MenACWY vaccines produced. In clinical trials, the capsular groups A and C components of these vaccines had over 90% effectiveness in the short term against disease caused by these organisms, but protection waned over time, especially among children. An intervention study in Quebec, Canada, showed that effectiveness of the group C component was 95% in children ≥6 years during the first 2 years post-vaccination, but was not effective in younger children. The group A component is immunogenic from a few months of age, therefore making it unlike other polysaccharide vaccines which do not induce protective immunity before 2 years of age. There are no protection data currently available for capsular group W or Y polysaccharides.

While these polysaccharide vaccines are effective in protecting older children and adults against disease, they are inadequate for young children with the highest disease incidence.

The immune response does not involve recruitment of helper T cells, so immunologi-

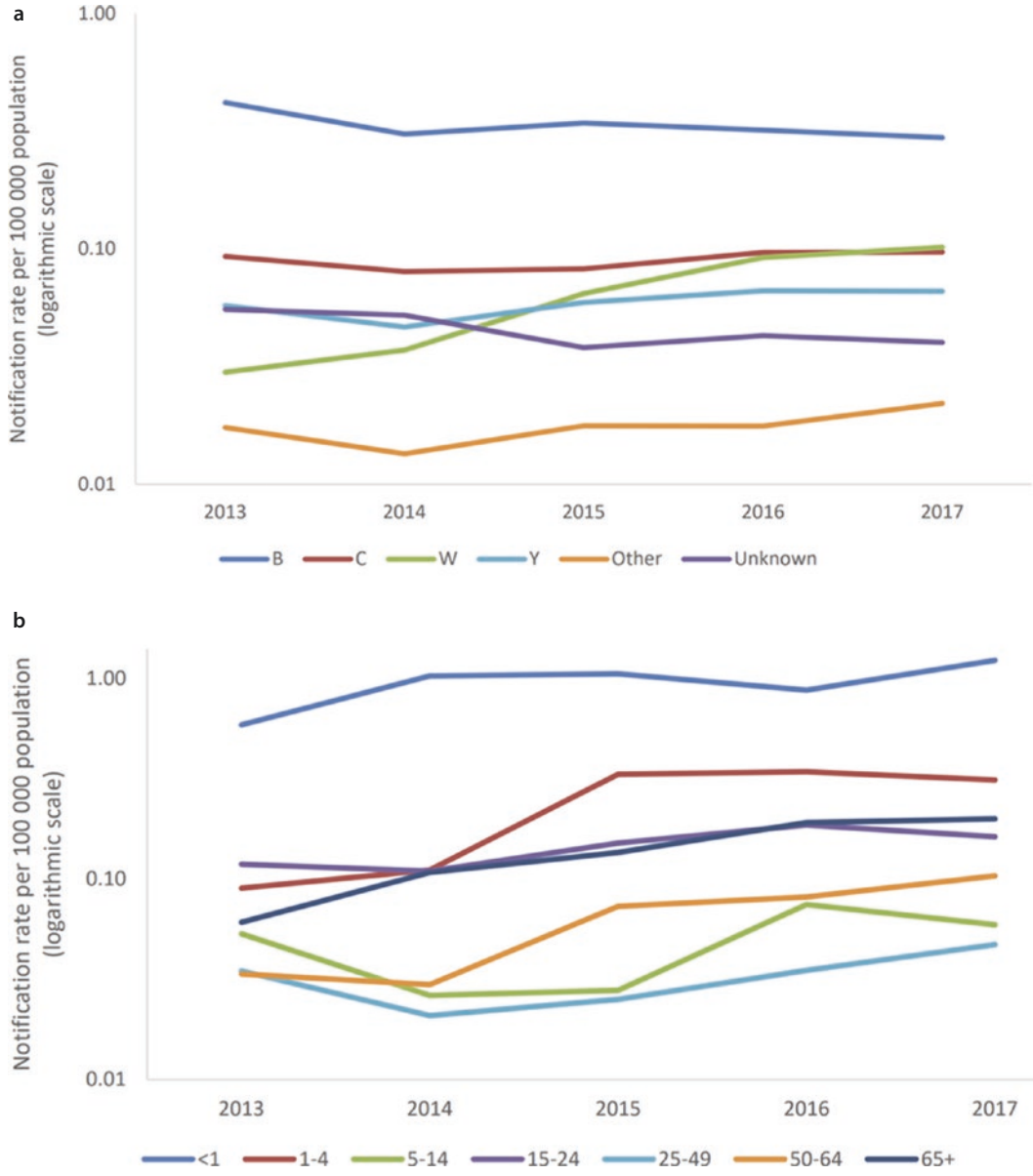


Fig. 22.1 **a** Notification rate of confirmed cases of invasive meningococcal disease by capsular group and year, EU/EEA, 2013–2017. **b** Notification rate of confirmed cases of invasive meningococcal disease caused by capsular group W by age group and year, EU/EEA, 2013–2017. *From Invasive Meningococcal Disease Surveillance Report; European Centre for Disease Prevention and Control 2019* (► https://www.ecdc.europa.eu/sites/default/files/documents/AER_for_2017-invasive-meningococcal-disease.pdf)

cal memory does not occur; the vaccines induce short-term protection only, are associated with immunological hyporesponsiveness (reduced responses after administration of booster doses), and do not elicit a response in children under 2 years of age. The lack of a response in young children is thought to be due to immaturity of the marginal zone B cells. Antibody responses to these vaccines are thought to be induced by cross-linking of the B-cell receptor by the repeating polysaccharide moieties, which results in differentiation of antigen-specific B cells into antibody-secreting cells without germinal centre forma-

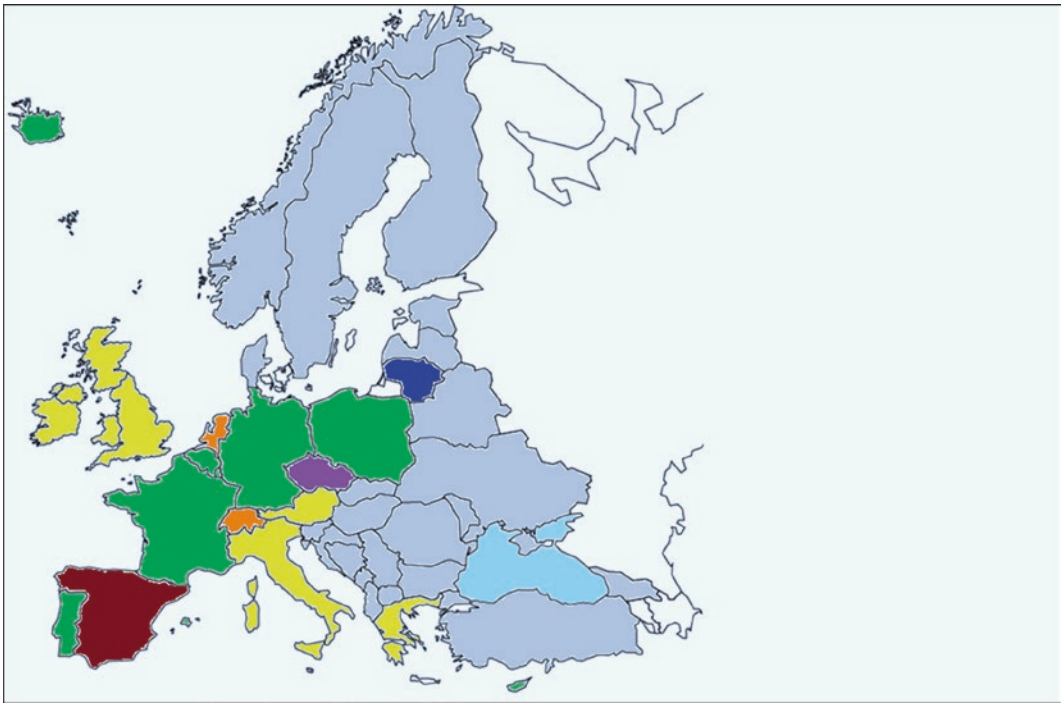


Fig. 22.2 Use of meningococcal vaccines in routine immunisation schedules across Europe as of January 2021. *Green* MenC vaccine only, *orange* MenACWY only, *dark blue* MenB only, *brown* MenC and MenACWY vaccines only, *purple* MenB and MenACWY vaccines only, *yellow* MenB, MenC and MenACWY vaccines, *grey* no meningococcal vaccine. This image only depicts vaccines in routine use; additional vaccines may be recommended in some countries in high-risk groups and/or travellers (Data from ▶ http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx and ▶ http://apps.who.int/immunization_monitoring/globalsummary/schedules (Accessed 26 January 2021)

tion in the draining lymph node. These vaccines have now almost entirely been replaced by protein-polysaccharide conjugate vaccines.

22.5 MenC Conjugate Vaccines

In the 1990s, conjugate vaccines, which are able to overcome the problems of plain polysaccharide vaccines, were successfully developed. In these products the polysaccharides are conjugated to protein carriers CRM_{197} (a non-toxic genetic variant of diphtheria toxin) (Meningitec, Nuron Biotech and Menjugate, GSK) or tetanus toxoid (NeisVac-C, Pfizer). The first monovalent MenC conjugate vaccines were licensed in the United Kingdom in 1999 and subsequently in the rest of Europe. The MenC conjugate vaccine was introduced into the UK routine immunisation programme from November 1999, and between 1999 and 2001 there was a reduction in MenC cases of 87% among the vaccinated groups (Fig. 22.3). The MenC conjugate vaccine induces high levels of bactericidal antibodies in all age groups, and vaccine effectiveness correlates with the induction of these functional antibodies with a titre ≥1:8 in the population.

In contrast to the polysaccharide vaccines, the MenC conjugate vaccines also induce immunological memory (eliciting an augmented response to subsequent doses of vaccine and/or the presence of MenC-specific memory B cells in the peripheral blood), which allow rapid (about 4 days) and high-magnitude responses to occur when a vaccinated individual is exposed to serogroup C meningococci. In unimmunised infants the response takes about 10 days and is of lower magnitude following their first dose of MenC

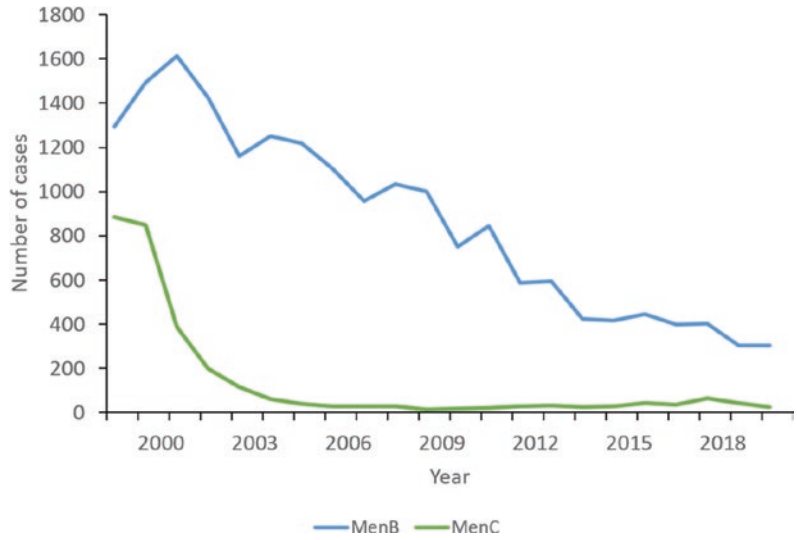


Fig. 22.3 Invasive meningococcal infections laboratory reports in England by capsular group and year, July 1998 to June 2020 (Source: Public Health England; ► https://www.gov.uk/government/publications/meningococcal-disease-laboratory-confirmed-cases-in-england-in-2019-to-2020)

vaccine. With the rapid onset of disease, however, this memory response within 4 days would not be sufficient to protect an individual, and maintenance of high levels of serum bactericidal antibody is likely to be necessary to preserve vaccine effectiveness.

22.6 Herd Immunity Induced by Conjugate Vaccines

The reduction in nasopharyngeal meningococcal carriage by conjugate vaccines has been a vital contribution to their remarkable success. The MenC conjugate vaccine in the United Kingdom reduced transmission of group C *N. meningitidis*, thereby providing herd protection – indirectly protecting unvaccinated individuals. After the vaccine was introduced, the number of cases among unvaccinated age groups fell by 67%, corresponding to a reduction in MenC carriage rates in vaccinated young adults. The highest rates of meningococcal carriage occur in adolescents and young adults, so many countries include an adolescent booster dose of MenC or MenACWY conjugate vaccine to maintain herd protection in the population, which will remain highly effective at maintaining protection of the population if high vaccine uptake rates can be maintained. A recent UK study reported a significant drop in carriage of *N. meningitidis* in adolescents aged 15–19 years – with overall carriage prevalence in 2014–2015 of 7%, compared with 17% to 19% in 1999–2001 – this was found in all capsular groups, except group Y and is likely due to a combination of vaccination programmes and changing social behaviours.

22.7 MenACWY Conjugate Vaccines

Three meningococcal ACWY (MenACWY) conjugate vaccines have been developed to provide broader protection against meningococcal disease (MenACWY polysaccharides conjugated to diphtheria toxoid, Menactra; tetanus toxoid, Nimenrix; or CRM197, Menveo), though only two are currently licensed in Europe (tetanus and CRM197 conjugate). Licensure trials undertaken with each of these products found them to be non-inferior in induction of bactericidal antibody when compared with either the previously licensed MenACWY conjugate vaccines, polysaccharide vaccines or the first-licensed MenACWY diphtheria conjugate vaccine. These vaccines, like the MenC conjugate vaccines, induce immunological memory, and the

Table 22.1 Licensed schedules of MenACYW in Europe

Population	Age	Dose series	Interval	Comments
Children in high-risk groups	0–12 months	2	≥1 month	Only MenACWY-TT licensed at this age, but others used off label in some countries where recommended
Unvaccinated children and high-risk groups	12 months to adulthood	1	N/A	MenACWY-TT licensed from 6 weeks of age and MenACWY-CRM from 24 months. Used for immunisation of toddlers and/or adolescents/adults in some countries. No data over 65 years of age

responses to the vaccines can be boosted. Currently only the tetanus conjugate vaccine is licensed for use in infants in Europe (from 6 weeks of age); the CRM197 conjugate is licensed from 2 years of age.

Potential scheduling of MenACWY vaccines could include a toddler dose as a replacement for the toddler MenC dose use in a number of countries and/or an adolescent dose, to act as a booster for earlier MenC doses (see Table 22.1) and to reduce nasopharyngeal carriage of meningococci among adolescents and disease caused by A, C, W and Y meningococci in these individuals and more widely though herd immunity. Serological evidence of protection has been shown to persist in most adolescents for at least 3–5 years after immunisation, but longer-term follow-up data are still needed. Antibody is not so well maintained after immunisation of younger children.

No prelicensure vaccine efficacy studies were undertaken, but one study estimated vaccine effectiveness over 6 years of use of the MenACWY–diphtheria -conjugate in the United States to be 69% (95% CI, 50–81%). There was an indication that the vaccine effectiveness declined from a high of 82% (54–923%) after the first year from immunisation, in keeping with observations of a decline in bactericidal antibody, leading the US policy to use a two-dose schedule of the vaccine. The MenACWY-CRM-197 conjugate vaccine was assessed in a study evaluating effectiveness of meningococcal vaccines against nasopharyngeal carriage in almost 3000 university students, and the vaccine was found to reduce carriage of C, W and Y strains by 36.2% (15.6–51.7), suggesting the potential for the vaccine to induce herd immunity.

Prelicensure trials showed the MenACWY conjugate vaccines to have a similar local and systemic reaction safety profile to that described for other conjugate vaccines and the licensed polysaccharide vaccines. Early reports of an association of the MenACWY–diphtheria conjugate vaccine with Guillain–Barre syndrome have not been confirmed in subsequent observations.

As a result of spread of a hyperinvasive clone of capsular group W meningococcus in the United Kingdom, immunisation of adolescents with MenACWY conjugate vaccine from age 13/14 to 18 years of age commenced in 2015, and during the first 12 months of the programme, there were 69% fewer group W meningococcal cases than predicted and no cases in vaccinated teenagers. 4CMenB, described below, has also been reported to provide protection against group W strains, based on data from England.

22.8 Capsular Group B Meningococcal Vaccines

The poor immunogenicity of the group B polysaccharide made the development of vaccines against MenB disease particularly challenging; however, the use of subcapsular proteins as alternative vaccine targets has enabled the recent development of two vac-

cines that offer the potential to overcome this gap in meningococcal disease prevention.

One of these, 4CMenB (Bexsero, GSK), has been included in the routine infant immunisation schedule in several countries and post-implementation data has confirmed that this vaccine is able to provide broad protection against capsular group B meningococcal disease in infants. The other, rLP2086 (Trumenba, Pfizer), is licensed for use in adolescents (age 10 years and older) in Europe and the United States.

22.9 4CMenB

This vaccine was licensed in Europe in 2013 and has subsequently been licensed in more than 35 countries. In Europe, 4CMenB is licensed from 2 months of age, with schedules differing according to age (Table 22.2).

4CMenB contains four key immunogenic components:

- Detoxified outer membrane vesicles (OMVs) from strain 44/76, within which the immunodominant antigen is porin A (PorA)
- Factor H–binding protein (fHbp)
- Neisserial adhesin A (NadA)
- Neisserial heparin–binding antigen (NHBA)

This multicomponent approach was taken to broaden the immunity against MenB provided by vaccines based on OMVs alone, which had been given in phase 3 effectiveness studies in Norway or in population-based interventions in Latin America, Normandy and New Zealand. These vaccines were effective against disease due to the strain from which the OMV was derived, but not against strains bearing variants of the immunodominant PorA protein (especially in infants). Their use was therefore confined to epidemics of MenB disease due to restricted lineages, rather than endemic disease. The use of the OMV in 4CMenB not only allowed inclusion of the PorA antigen, but may also non-specifically enhance the immune response to the additional vaccine antigens.

Of the 'additional' proteins, fHbp and NHBA are nearly universal on pathogenic *N. meningitidis*, while genes for NadA were present in 23% of a European strain panel. Clinical trials in which 6427 participants from 2 months to adulthood received 4CMenB have shown these proteins induce bactericidal antibodies against MenB strains expressing closely matched antigens. However, pathogenic meningococci differ in the surface expression of these proteins, and like PorA, there is phenotypic variability that potentially restricts the breadth of cross-pro-

Table 22.2 Licensed schedules of 4CMenB in Europe

Population	Age	Dose series	Interval	Booster recommended
Infants	2–5 months	3	≥1 month	One dose at 12–23 months
Unvaccinated infants	6–11 months	2	≥2 months	One dose at 12–23 months; ≥2 months from primary series
Unvaccinated children	12–23 months	2	≥2 months	One dose 12–23 months after the primary series
Unvaccinated children	2–10 years	2	≥2 months	
Adolescents and adults	11 years and older	2	1–2 months	

tection afforded by the antibodies induced by each individual vaccine component. Determining the likely breadth of direct protection afforded by immunisation with 4CMenB in any given population has to take into account all these factors, even before considering the potential for synergistic (or antagonistic) interactions between different vaccine-induced antibodies acting on the target bacteria at the same time.

Given these challenges, various methods have been used to predict the proportion of MenB disease potentially preventable by immunisation with 4CMenB. One of these, 'MATS', predicts that the potential coverage of 4CMenB in Europe varies by country between 73% and 85%. In England coverage by MATS was predicted to be 67.2% in 2014/2015, a fall from 73% in 2007/2008, whereas 88% of common disease-causing strains appeared susceptible to pooled post-immunisation sera. While still awaiting formal validation by comparison with the emerging 'real-life' effectiveness data, these estimates have provided a starting point for consideration of the potential benefits and cost-effectiveness of the vaccine's introduction.

22.9.1 Experience of Use

Use of 4CMenB was initially restricted to outbreaks of MenB disease in the Saguenay–Lac-Saint-Jean region of Quebec, Canada, in educational institutions in the United States and Canada until it was introduced into the routine immunisation schedules in the United Kingdom and subsequently several countries across Europe. Many additional countries have also recommended the use of 4CMenB for children with complement deficiencies and splenic dysfunction/asplenia. In the United Kingdom, routine immunisation at 2, 4 and 12 months commenced in September 2015 (for infants born after 1 May 2015). Ten months into this immunisation campaign, 95.5% and 88.6% of eligible infants had received their first and second dose (respectively) by 6 months of age. Lower 4CMenB immunisation rates in infants experiencing disease compared with their age-matched population cohort suggested a vaccine effectiveness of 82.9% (95% C.I. 24.1–95.2), and the number of MenB disease cases in the vaccine-eligible age group was 50% lower in the period following vaccine introduction than the average of the previous 4 years. After 3 years of the UK programme, there has been a 75% reduction in all MenB disease in age groups that were fully eligible for vaccination.

22.9.2 Reactogenicity/Safety

The most significant adverse events after immunisation of infants are fever and irritability, which are observed in approximately 60% and 75% of 2-month-old infants when 4CMenB is given with routine infant vaccines (DTaP–IPV–HepB and 7-valent pneumococcal vaccine). These relatively high rates of fever may be due to the inclusion of OMVs in this vaccine. Rates of fever were reduced by the use of prophylactic paracetamol at the time of immunisation (from 71% to 52% in 2-month-olds) without impacting on the vaccine's immunogenicity. Other reported reactions include tenderness at the injection site, which is reported as severe in 12–16% of infants (crying when moving leg) and 17% of adolescents (unable to perform unusual duties).

Concerns regarding the rates of post-immunisation fever in infants led to the recommendation in the United Kingdom that prophylactic paracetamol be administered at the time of 4CMenB administration for 2- and 4-month-olds, with two further doses given in the next 24 h. Despite this there was an increase in emergency department attendances for post-immunisation reactions.

22.9.3 Areas of Uncertainty

Two key determinants of the impact of 4CMenB immunisation campaigns that are as yet unknown are the duration of vaccine-induced immunity and whether such campaigns can induce herd immunity by reducing rates of nasopharyngeal carriage of potentially invasive MenB strains.

Following immunisation in infancy with three priming doses and boosting at 12 months of age, over 97% of children have bactericidal antibodies above the accepted correlate of protection for three key MenB strains, and it is from this presumed peak concentration that estimates of vaccine coverage have been made. By 4 years of age, these proportions had fallen to 9%, 12% and 93%, depending on which strain was tested. Although a good response to a booster dose was observed, an additional booster dose is not included in the licensed 4CMenB schedule. Whether this waning of antibodies against some vaccine antigens will be of clinical relevance as children proceed through their school years and into adolescence will only be apparent from ongoing disease surveillance in an immunised population.

A recent large cluster randomised trial in Australia found no effect of 4CMenB on carriage of disease-causing meningococci, highlighting that the benefit of this vaccine is likely to be via direct protection.

22.10 Bivalent rLP2086

This vaccine is licensed for use in adolescents in the United States in a three-dose (0, 1–2, 6 months) or two-dose (0, 6 months) schedule, the former being more appropriate in outbreak settings. As with 4CMenB, this vaccine has a 'category B' recommendation for use in 16- to 23-year-olds in that country (i.e. may be administered to provide short-term protection against most strains of serogroup B meningococcal disease). An application for licensure in the European Union in those 10 years and was approved.

This vaccine is based on two variants of the fHbp protein that have had a lipid tail attached. As with 4CMenB, immunogenicity against a broad range of MenB strains has been demonstrated, and the vaccine has been licensed on this basis rather than on direct evidence of effectiveness.

Bivalent rLP2086 has been used in the context of college outbreaks in the United States; however, formal effectiveness studies have not been possible during these campaigns due to the low number of cases and brief duration of the outbreaks. No impact of vaccination on nasopharyngeal carriage was observed during an outbreak at Providence College, Rhode Island in 2015, however the relatively small sample size did not allow a definitive assessment of this vaccine's potential to induce herd immunity.

Observed side effects following bivalent-rLP2086 administration to adolescents include injection site pain (severe in 8.2%), headache (56.9%, severe in 1.4%) and pyrexia (8.3%). Serious adverse events in clinical trials were no more common following this MenB vaccine than comparator, licensed, vaccines. The 'Be on the TEAM' (Teenagers Against Meningitis) Study is a pragmatic, partially randomised controlled trial of 24,000 students aged 16–19 years in their penultimate year of secondary school across the UK with regional allocation to a 0 + 6-month schedule of 4CMenB or MenB-fHbp or to a control group – to provide data on the impact of these vaccines on carriage.

22.11 Conclusion

The availability of vaccines against MenC, MenACWY and MenB disease represents an important advance in the prevention of meningococcal disease. The dramatic changes in meningococcal epidemiology observed over the last two decades in Europe emphasise the need to have vaccines available to deal with existing and emerging threats in a timely manner to save lives. Further developments such as the recent emergence of serogroup X in sub-Saharan Africa, for which there is currently no licensed vaccine, demonstrate that vaccine prevention of meningococcal disease is an ongoing and evolving challenge.

Further Reading

Agnememel A, Hong E, Giorgini D, Nunez-Samudio V, Deghmane AE, Taha MK. Neisseria meningitidis Serogroup X in Sub-Saharan Africa. Emerg Infect Dis 2016;22(4):698–702.

Artenstein MS, Gold R, Zimmerly JG, Wyle FA, Schneider H, Harkins C. Prevention of meningococcal disease by group C polysaccharide vaccine. N Engl J Med 1970;282(8):417–20.

Bjune G, Hoiby EA, Gronnesby JK, Arnesen O, Fredriksen JH, Halstensen A, Holten E, Lindbak AK, Nokleby H, Rosenqvist E, et al. Effect of outer membrane vesicle vaccine against group B meningococcal disease in Norway. Lancet 1991;338(8775):1093–6.

Borrow R, Balmer P, Miller E. Meningococcal surrogates of protection–serum bactericidal antibody activity. Vaccine 2005;23(17–18):2222–7.

Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis. Lancet Infect Dis 2010;10(12):853–61.

Cohn AC, MacNeil JR, Clark TA, Ortega-Sanchez IR, Briere EZ, Meissner HC, Baker CJ, Messonnier NE, Centers for Disease and Prevention. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2013;62(RR-2):1–28.

European Centre for Disease Prevention and Control. Surveillance atlas of infectious disease. Accessed 26th Jan 2021.

Frosi G, Biolchi A, Lo Sapio M, Rigat F, Gilchrist S, Lucidarme J, Findlow J, Borrow R, Pizza M, Giuliani MM, Medini D. Bactericidal antibody against a representative epidemiological meningococcal serogroup B panel confirms that MATS underestimates 4CMenB vaccine strain coverage. Vaccine 2013;31(43):4968–74.

Jafri RZ, Ali A, Messonnier NE, Tevi-Benissan C, Durrheim D, Eskola J, Fermon F, Klugman KP, Ramsay M, Sow S, Zhujun S, Bhutta ZA, Abramson J. Global epidemiology of invasive meningococcal disease. Popul Health Metr 2013;11(1):17.

Kelly C, Arnold R, Galloway Y, O'Hallahan J. A prospective study of the effectiveness of the New Zealand meningococcal B vaccine. Am J Epidemiol 2007;166(7):817–23.

Kelly DF, Snape MD, Clutterbuck EA, Green S, Snowden C, Diggle L, Yu LM, Borkowski A, Moxon ER, Pollard AJ. CRM197-conjugated serogroup C meningococcal capsular polysaccharide, but not the native polysaccharide, induces persistent antigen-specific memory B cells. Blood 2006;108(8):2642–7.

Ladhani SN, Andrews N, Parikh SR, Campbell H, White J, Edelstein M, Bai X, Lucidarme J, Borrow R, Ramsay ME. Vaccination of Infants with Meningococcal Group B Vaccine (4CMenB) in England. NEJM 2020;382:309–317

Ladhani SN, Campbell H, Andrews N, Parikh SR, White J, Edelstein M, Clark SA, Lucidarme J, Borrow R, Ramsay ME. First real-world evidence of meningococcal group B vaccine, 4CMenB, protection against meningococcal group W disease; prospective enhanced national surveillance, England, Clin Inf Dis 2020; https://doi.org/10.1093/cid/ciaa1244

Ladhani SN, Giuliani MM, Biolchi A, Pizza M, Beebeejaun K, Lucidarme J, Findlow J, Ramsay ME, Borrow R. Effectiveness of Meningococcal B Vaccine against Endemic Hypervirulent Neisseria meningitidis W Strain, England, Emerg Infect Dis 2016;22(2):309–11.

Maiden MC, Stuart JM, U. K. M. C. Group. Carriage of serogroup C meningococci 1 year after meningococcal C conjugate polysaccharide vaccination. Lancet 2002;359(9320):1829–31.

Marshall HS, McMillan M, Koehler AP, Lawrence A, Sullivan TR, MacLennan JM, Maiden MCJ, Ladhani SN, Ramsay ME, Trotter C, Borrow R, Finn A, Kahler CM, Whelan J, Vadivelu K, Richmond P. Meningococcal B Vaccine and Meningococcal Carriage in Adolescents in Australia. NEJM 2020;382:318–327

Nainani V, Galal U, Buttery J, Snape MD. An increase in accident and emergency presentations for adverse events following immunisation after introduction of the group B meningococcal vaccine: an observational study. Arch Dis Child 2017;102:958–962.

Peltola H, Makela H, Kayhty H, Jousimies H, Herva E, Hallstrom K, Sivonen A, Renkonen OV, Pettay O, Karanko V, Ahvonen P, Sarna S. Clinical efficacy of meningococcus group A capsular polysaccharide vaccine in children three months to five years of age. N Engl J Med 1977;297(13):686–91.

Read RC, Baxter D, Chadwick DR, Faust SN, Finn A, Gordon SB, Heath PT, Lewis DJ, Pollard AJ, Turner DP, Bazaz R, Ganguli A, Havelock T, Neal KR, Okike IO, Morales-Aza B, Patel K, Snape MD, Williams J, Gilchrist S, Gray SJ, Maiden MC, Toneatto D, Wang H, McCarthy M, Dull PM, Borrow R. Effect of a quadrivalent meningococcal ACWY glycoconjugate or a serogroup B meningococcal vaccine on meningococcal carriage: an observer-blind, phase 3 randomised clinical trial. Lancet 2014;384(9960):2123–31.

Sierra GV, Campa HC, Varcacel NM, Garcia IL, Izquierdo PL, Sotolongo PF, Casanueva GV, Rico CO, Rodriguez CR, Terry MH. Vaccine against group B Neisseria meningitidis: protection trial and mass vaccination results in Cuba. NIPH Ann 1991;14(2):195–207; discussion 208–10

Snape MD, Dawson T, Oster P, Evans A, John TM, Ohene-Kena B, Findlow J, Yu LM, Borrow R, Ypma E, Toneatto D, Pollard AJ. Immunogenicity of two investigational serogroup B meningococcal vaccines in the first year of life: a randomized comparative trial. Pediatr Infect Dis J 2010;29(11):e71–9.

Snape MD, Perrett KP, Ford KJ, John TM, Pace D, Yu LM, Langley JM, McNeil S, Dull PM, Ceddia F, Anemona A, Halperin SA, Dobson S, Pollard AJ. Immunogenicity of a tetravalent meningococcal glycoconjugate vaccine in infants: a randomized controlled trial. JAMA 2008;299(2):173–84.

Trotter CL, Andrews NJ, Kaczmarski EB, Miller E, Ramsay ME. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. Lancet 2004;364(9431):365–7.

Vieusseux M. Memoire sur le maladie qui a regne a Geneva au printemps de 1805. J Med Clin Pharm 1805;11:163–82.

Paediatric Vaccines for Travel Outside Europe

Natalie Prevatt and Ron H. Behrens

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_23

23.1 Routine Childhood Vaccination for Travel

Prior to international travel, the routine childhood immunisation schedule must be up to date, and vaccines may be brought forward if necessary, so that essential vaccines and boosters are not missed during travel. This is particularly important for MMR and DTP since the risk of contracting these infections is much higher in the tropics than in many parts of Europe. Some vaccines can be brought forward as early as 6 weeks of age. See Table 23.1.

MMR can be given as early as 6 months (with the routine dose at 12 months still to be given in such circumstances). A minimum vaccine interval of 4 weeks must be maintained for all accelerated vaccines.

Influenza is also an important vaccine for travel, as seasonal influenza is the commonest vaccine preventable disease in travellers, but this is covered elsewhere.

23.2 Travel-Specific Vaccination: An Introduction

A wide range of travel vaccines exist, but it is important to consider the need for vaccination, and balance the risk of disease against the risk associated with the vaccine, and to consider how long it takes to become effective.

Table 23.1 Accelerated schedules for routine vaccinations in paediatric travel

Vaccination	Earliest age of vaccination
DTP	6 weeks
MMR	6 months (up to 11 months. Should be followed by routine MMR at 12 months of age)
Hib	6 weeks
IPV	6 weeks
PCV13	6 weeks
Hep B	From birth

Hepatitis A virus is a good illustration of this. It causes an estimated 1.4 million infections per year. It is transmitted by ingestion of food and water contaminated with faeces, and occasionally by close contact between children. As such the distribution of Hepatitis A is closely mapped to poor economic and sanitary conditions, with the highest incidence in the Indian subcontinent. In some places the presence of Hepatitis A antibody from natural infection is close to 100%. Children who have already had Hepatitis A disease, or are likely to suffer only mild illness (those ≤5 years of age), may not need this vaccine. In well children under 5 years the main concern is of passing the virus on to older children and adults on return from the travel, since shedding may continue for up to 6 weeks. Ideally, vaccination against Hepatitis A should be given 14 days prior to travel to become fully effective (see Chap. 12 for more details on Hepatitis A).

An individualised risk assessment is thus essential for every paediatric traveller. This should involve the time available ahead of their journey, and all aspects of the child's health including any pre-existing health issues, which may influence vaccination response and efficacy.

23.3 Travel Vaccinations in Children

23.3.1 Yellow Fever

The Yellow Fever (YF) virus is an arthropod-borne flavivirus, which circulates between monkeys and humans, and between humans, via *Aedes* species of mosquitoes.

The risk of YF is present in parts of South America (plus Trinidad) and sub-Saharan Africa (see Image 23.1a, b).

Yellow Fever (YF) ranges from a moderate viral illness with nausea and vomiting to a severe, multisystem haemorrhagic disease, with jaundice (hence the name) and circulatory shock. Approximately one-quarter of patients die within 7–10 days of onset. Those patients who survive will have acquired lifelong immunity.

Global numbers estimate approximately 200,000 cases with between 30,000 and 180,000

23

Image 23.1 **a** Yellow fever distribution in Central and South America. Jentes ES, Poumerol G Fau – Gershman MD, Gershman Md Fau – Hill DR, Hill Dr. Fau – Lemarchand J, Lemarchand J Fau – Lewis RF, Lewis Rf Fau – Staples JE, et al. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for Yellow Fever. (1474–4457)
► http://www.who.int/ith/en/
► http://gamapserver.who.int/mapLibrary/Files/Maps/ITH_YF_vaccination_americas.png?ua=1
Yellow fever vaccine recommendations in the Americas 2013 WHO map of YF in the Americas and Africa
► http://apps.who.int/ithmap/
b Yellow fever distribution in Africa. (Jentes ES, Poumerol G Fau – Gershman MD, Gershman Md Fau – Hill DR, Hill Dr. Fau – Lemarchand J, Lemarchand J Fau – Lewis RF, Lewis Rf Fau – Staples JE, et al. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for Yellow Fever. (1474–4457))
► http://gamapserver.who.int/mapLibrary/Files/Maps/ITH_YF_vaccination_africa.png?ua=1
Yellow fever vaccination recommendations in Africa, 2015

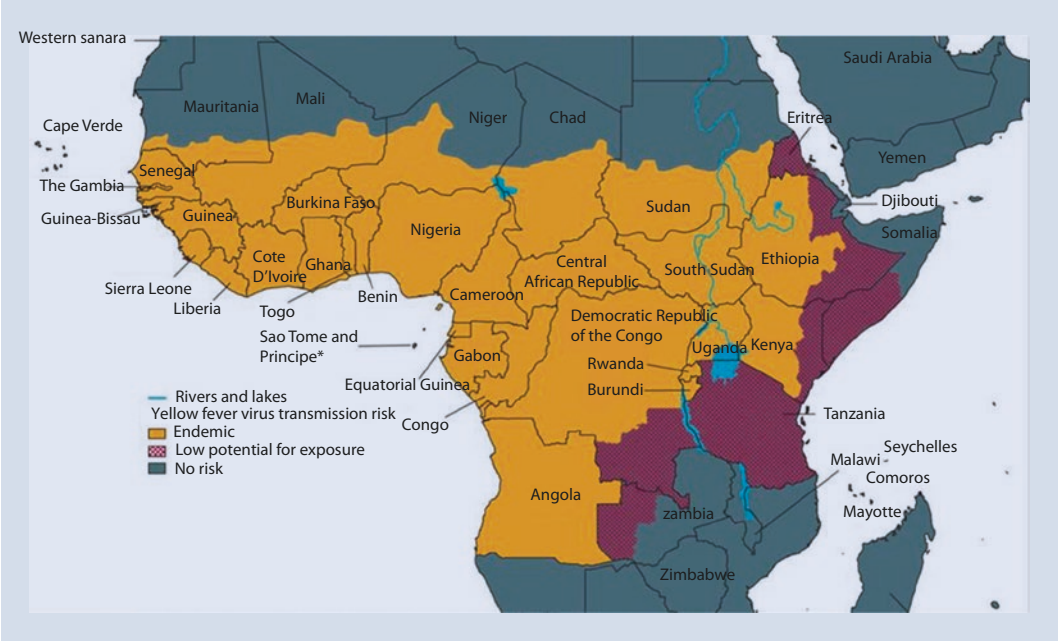


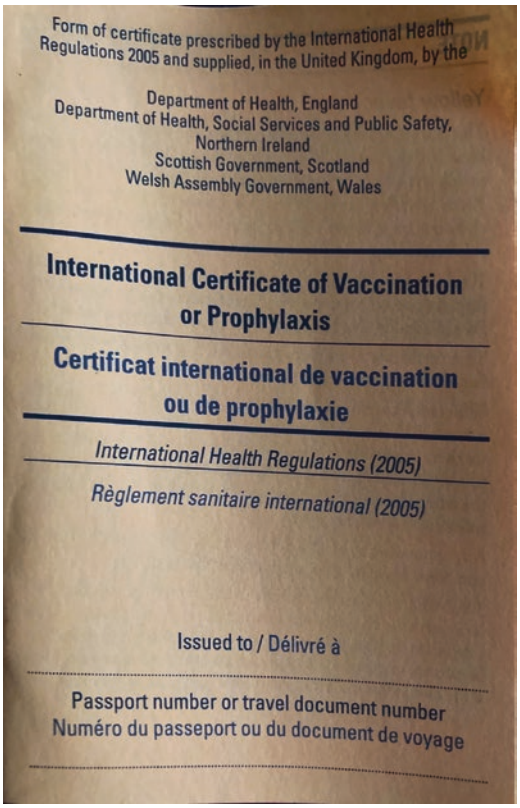
Image 23.1 (continued)

fatalities per annum. The number of cases reported to World Health Organization (WHO) are clearly not indicative of the risk faced by travellers however, as very few travellers are infected with yellow fever. There are only 21 reported travel-acquired cases since 1970. More than half (11) of these were in travellers to an outbreak in Brazil, highlighting the importance of counselling against unvaccinated travel to outbreak situations and of attending a travel medicine clinic with up-to-date information on disease outbreak surveillance.

Vaccine Requirements for Paediatric Travellers

The requirement for YF vaccine by destination is outlined in the WHO's International Health Regulations (IHRs), and children and infants aged over >9 months should receive the vaccine based on this indication, after a risk–benefit analysis which takes into account their journey and likely exposure.

The IHRs are designed to prevent the spread of the virus from endemic to non-endemic regions through travel. An international certificate of vaccination (see Image 23.2: yellow card) may, therefore, be required both by


Form of certificate prescribed by the International Health Regulations 2005 and supplied, in the United Kingdom, by the

Department of Health, England
Department of Health, Social Services and Public Safety, Northern Ireland
Scottish Government, Scotland
Welsh Assembly Government, Wales

International Certificate of Vaccination or Prophylaxis

Certificat international de vaccination ou de prophylaxie

International Health Regulations (2005)

Règlement sanitaire international (2005)

Issued to / Délivré à

Passport number or travel document number
Numéro du passeport ou du document de voyage

Image 23.2 'Yellow Card' Certificate. (Full example at ► https://www.who.int/ihr)

endemic and non-endemic countries under these regulations. Thus, the requirement for a YF vaccine certificate may not reflect the risk of exposure in that country.

There are three scenarios where travellers, including children, may need to receive the YF vaccine:

- Travelling to countries with YF transmission.
- Travelling to countries requiring YF vaccination for those arriving from countries with risk of YF transmission.
- Travelling to countries requiring mandatory YF vaccination for travellers from all countries.

This is an important factor to consider where relative contraindications to the vaccination apply. The list of each countries requirements for the YF vaccination certificate (or exemption certificate) can be found online on the WHO website. The vaccine must be given more than 10 days prior to entry to comply with the International Health Regulations (IHRs), as the neutralising antibody response will have been achieved in this timescale.

23.3.2 Paediatric Yellow Fever Vaccination

Two vaccines of different strains, 17DD, and 17D-204, were developed simultaneously in the 1930s and are thought to have similar immunogenicity and safety profiles. Currently the only licenced YF vaccine used in Europe is Stamaril®, made by Sanofi Pasteur. It is a live attenuated 17D-204 strain of yellow fever virus, grown in embryonated chick eggs. Every 0.5 ml dose contains at least 1000 IU, which should cause a subclinical infection in healthy individuals. The dose is 0.5 ml regardless of age.

The vaccine is administered as an intramuscular (IM) or deep subcutaneous injection.

This vaccine is highly effective. At 10 days after vaccination, 90% of adults have seroconverted; at 1 month, nearly 100% are protected. Paediatric studies show less seroconversion, with a minimum seroconversion rate of 86% after single-dose vaccination, and the lowest seroconversion rates are in children 9–36 months of age.

A neutralising antibody titre of 1:10 is considered protective against YF, yet neutralising antibody testing may underestimate protection because T-cell memory response is important to long-term protection.

Vaccine recipients maintain detectable levels of neutralising antibody for more than 10 years post vaccination. In 2016, the World Health Organization (WHO) amended the 10-year booster rule dictating that a single dose of vaccine in adults should now be considered to confer lifelong protection and no further boosters are required, unless the recipient was immunocompromised or below 2 years at the time of vaccination.

Once a child over age 2 has been vaccinated, his or her immunity is considered to be lifelong, and the Yellow Card is valid as a lifelong certification according to IHRs. Children vaccinated while aged between 6 months and 2 years will require a booster before travel to an endemic country if that travel takes place more than 10 years after the initial vaccine.

There is evidence in adults and children over 2 years that a fractional dose of the vaccine administered as 0.1 ml IM produces equivalent neutralising antibody titres. Persistence of long-term antibodies has not been demonstrated in an RCT setting and so while this method can be used where there is a shortage of vaccine in outbreak situations, currently WHO does not allow certification when fractional dosing is used.

YF vaccine should not be given to infants aged less than 6 months due to the risk of vaccine-associated encephalitis. YF vaccine can be considered between for infants aged 6–9 months where there is a high risk, for example in outbreak settings.

The vaccine should similarly only be given to pregnant or breastfeeding mothers under such high-exposure circumstances as visiting a region with an outbreak. There are several reports of serious vaccine associated side effects in infants of mothers who had received YF vaccination during breastfeeding. The risks and benefits of maternal breastfeeding need to be discussed when planning to admin-

ister YF vaccine. There is currently insufficient evidence to recommend expressing and discarding breast milk post vaccination.

23.3.3 Yellow Fever Vaccine Side-Effect Profile

Only registered centres are authorised to give YF vaccine in most countries.

A range of temporary adverse events have been reported following the administration of YF vaccine. The most frequent reactions include headache, myalgia and injection site swelling, which occur in 10–15% of recipients. In infants and young children, the most frequently reported reactions are irritability, crying and appetite loss, and these are reported in approximately one-third of children in the first few days. Pyrexia can develop up to 14 days afterwards. Reports of generalised allergic reactions indicate an incidence of 1 in 131,000.

However, YF can also rarely cause Severe Adverse Events (SAEs): There are two distinct clinical presentations of YF Severe Adverse Events. They have predominantly been associated with recipients of the primary dose of the vaccine. They are Yellow Fever vaccine–associated viscerotropic disease (YEL-AVD) and Yellow Fever vaccine–associated neurologic disease (YEL-AND).

YEL-AVD usually occurs within 10 days of vaccination. Features resemble fulminant infection by wild-type virus and thus may include fever, fatigue, myalgia, headache and jaundice. This may progress to hypotension, metabolic acidosis, muscle and liver cytolysis, cytopenia, and renal and respiratory failure. In these cases, YF vaccine can be detected in serum and tissue PCR. The mortality rate has been around 60%. The risk of YEL-AVD in travellers is estimated to be 1 per 250,000 primary vaccinees, with the highest risk in those over the age of 60 years where it occurs in approximately 1:50,000. Cases of YEL-AVD in children appear to be extremely rare.

YEL-AND usually occurs within a month of vaccination, and is the more likely SAE presentation in children. Features include high fever and headache, which may progress to one or more of confusion, encephalitis, meningitis, focal neurological deficit, or Guillain-Barré syndrome. Approximately one-third of cases have been fatal, but in survivors the neurological sequelae may be longstanding and disabling. Encephalitis is a particular risk in those under 9 months of age, with multiple cases of YEL-AND described in infants less than 7 months old, prior to the establishment of a minimum age for vaccination. The incidence among infants aged below 6 months is the highest and has been estimated as more than 0.5 cases per 1000. Cases of YEL-AND have also occurred following transmission from nursing mothers to infants.

Contraindications to YF Vaccine

YF vaccine can only be administered by designated clinics licensed by the health administration for the territory, and designated YF centre status is contingent on meeting the safety standards necessary to give this vaccine, one of which is staff training.

Table 23.2 denotes absolute and relative contraindications to the vaccine for your information. Children with any of the contraindications listed are at risk of vaccine-associated disease and should be provided a letter of exemption for authorities, and the parents advised to use stringent bite prevention methods when in a YF endemic zone.

YF vaccine is grown in chicken embryos and contains approximately 16 mcg of ovalbumin per dose. Children with anaphylactic allergy to egg, requiring previous intensive care, should not receive this vaccine as the risk of anaphylaxis outweighs the benefit of vaccination. Children with moderate and mild egg allergy can receive this vaccine if necessary, in a clinical setting where expertise and equipment for resuscitation is available.

Summary of Recommendations

Children should be given this vaccine for travel to areas where YF certification is required for entry, unless they have a contraindication or precaution. Where these exist, an exemption certificate should be issued to meet certification requirements.

Table 23.2 Absolute and relative contraindications to YF vaccination

Contraindications in children	Precautions in children
Age < 6 months. Symptomatic HIV infection or CD4 < 200 (or < 15% of the total in children <6 years). Anaphylaxis to vaccine components (e.g. egg or gelatine). Thymus disorders (including thymoma/thymectomy/absent thymus/DiGeorge syndrome). Primary immunodeficiency. Malignancy. Post organ transplantation or post HSCT. Immunosuppressive therapy including high-dose steroids for more than 2 weeks within past month[a]	Age 6–9 months. Asymptomatic HIV infection and (or CD4 15–24% of total in children <6 years). Allergy to vaccine components. Current febrile illness. Low dose steroids more than 2 weeks within past month[b,c]

[a]Yellow fever vaccine should not be given to individuals on high-dose systemic steroids. They should have discontinued therapy at least 1 month before the vaccine

[b]In patients taking low-dose steroids, yellow fever can be used with caution. Low-dose steroid therapy is usually defined as up to 20 mg prednisolone (or equivalent) per day in an adult or 1 mg/kg/day in children under 20 kg for more than 14 days. Those on low doses in combination with oral non-biological immune modulating drugs (e.g. methotrexate) may be able to receive this vaccine, but specialist advice should be sought

[c]Physiological replacement therapy and steroid in the form of topical, standard inhaled, ophthalmic and intra-articular/tendon injections do not constitute a risk

23.4 Rabies

Rabies is widespread across Asia, Africa, America, Europe, and the Middle East, with the highest incidence of human infections reported from India.

Rabies is caused by a *Lyssavirus*, which is transmitted to humans through the bites or scratches of infected mammals including, but not exclusively, dogs, cats and bats. Dog saliva is the most frequent source of rabies infection, accounting for 99% of rabies deaths in the last decade. The highest burden of exposures is among children, with 40% of post-exposure attendances being for children who have been bitten.

The incubation period from infected bite to disease varies from weeks to years. The first symptoms are fever, pain and paraesthesia around the wound. As the rabies virus spreads through the nervous system it results in encephalitis, often with an associated neuropathy or paralysis, then death. Other infamous symptoms of rabies encephalitis are aggression, aerophobia and hydrophobia. Children become symptomatic earlier, as, on account of their stature, they are more likely to be bitten on the face or head, and thus closer to the brain. Once symptoms develop rabies is invariably fatal.

23.4.1 Epidemiology of Rabies in Travellers

Rabies causes an estimated 59,000 deaths per annum globally but cases in travellers are rare. Some estimates in travellers suggest 0.4% of adult travellers experience a potential rabies exposure per 1-month stay in an endemic country.

Vaccine Indications for Paediatric Travellers

A course of pre-exposure rabies vaccine should be considered for children who take multiple visits to, or have prolonged stays in, countries where rabies is endemic. A 'pro-

longed visit' is often considered to be a stay of over 1 month. WHO affirms however that the risk assessment for this vaccine should not be based solely on length of stay. Activities such as running and cycling also place individuals at higher risk. Children are at particularly high risk when petting or stroking feral animals. It is not usual to recommend vaccination for not ambulant infants, as they are unlikely to come into contact with animals.

Parents should be encouraged to decide on whether to vaccinate their children by balancing the cost of a course of rabies vaccine (~$200–$500) with the cost of disruption of their trip following a potential exposure to seek a course of a post-exposure prophylaxis (PEP), often only available in major cities.

Availability and cost make Human Rabies Immunoglobulin (HRIG) difficult to obtain in many low-income countries. When a PEP course including human rabies immunoglobulin (HRIG) is required after a bite, the lack of availability can result in premature return home to obtain treatment. Rabies vaccine may thus be viewed as insurance, as accessing RIG during travel can prove very costly and time-consuming.

23.4.2 Paediatric Rabies Vaccination

There are two licenced rabies vaccines available in Europe:

- Human diploid cell vaccine.
- Purified chick embryo cell vaccine.

The human cell culture vaccine is a Wistar rabies virus strain (PM/WI 38–1503-3 M) grown in human diploid cells, ultra-filtrated and inactivated. The chick embryo vaccine is prepared from a Flury LEP strain grown in chicken embryoblasts, centrifuged and inactivated. This version contains <16 mcg of ovalbumin per dose.

The pre-exposure rabies vaccine schedule (the primary course) consists of three doses of vaccine at day 0, 7 and 28, intramuscularly. The third dose can be given early at day 21 if there is insufficient time before travel, and this appears to have no significant effect on immunogenicity. An accelerated rapid schedule on days 0, 3 and 7 (with a booster at 1 year) is licensed for both formulations of vaccine. Restarting an interrupted vaccine course is unnecessary.

The protective antibody level for rabies is estimated to be >0.5 IU/ml; however, there is no rational for serological testing a traveller post vaccination, unless to confirm seroconversion in an immunosuppressed individual.

The 28-day course in adults provides a 95% seroconversion rate and anti-rabies antibodies are long-lived. There is, however, a paucity of data in the paediatric population.

Intradermal vaccination is also effective in producing seroconversion and is cheaper (0.1 ml dose, compared to 1.0 ml) to administer. This intradermal use of vaccine is approved by WHO but remains 'off-licence' in much of Europe. There are inherent technical difficulties with giving vaccines effectively into the dermis. This should only be given by skilled practiced technicians.

Post-exposure Prophylaxis (PEP)

Individuals who have received a full pre-exposure course of rabies *will* still require further rabies vaccine doses following a potential infection. However the pre-exposure course eliminates the need for administering HRIG, which is in short global supply.

The use of both PEP and RIG depends on the nature of the exposure (Table 23.3). The number of PEP vaccine doses required post-exposure is dependent on the pre-exposure vaccine status. Travellers who have had a full 21- or 28-day course of pre-exposure vaccine will require just two booster doses of vaccine. Travellers who have not had any pre-exposure vaccination will require up to six doses of vaccine (depending on the PEP regimen).

Children with category III exposures who have not received a full course of pre-exposure rabies will require passive immunisation with Human Rabies Immunoglobulin (HRIG) in addition to the post-exposure vaccine course.

Rabies immunoglobulin is an IgG preparation extracted from the plasma of hyper-immunised individuals. Aside from the risks

Table 23.3 Classifying rabies risk for the use of PEP

WHO category of exposure	
Category I	Licks to intact skin whilst feeding/touching (i.e. no exposure): *No PEP required*
Category II	Nibbling of skin, minor scratches or abrasions without bleeding: *Immediate PEP required*
Category III	Transdermal bites or scratches, licks on broken skin, contamination of mucous membranes with saliva from licks, exposure to bats: *Immediate PEP required PLUS administration of Rabies Immunoglobulin (RIG) is required for unvaccinated children*

associated with blood-borne products, RIG is difficult to access and costly in endemic countries, and the shortage of RIG is an important part of the risk analysis.

In Southeast Asia, where there was a regional strategy to eliminate rabies deaths by 2020, an equine immunoglobulin is sometimes available. However, this formulation is associated with a significant risk of serum sickness and hypersensitivity reactions.

The decision to give vaccine and PEP after an exposure in vaccine allergic individuals should be weighed carefully, and the vaccine given with preparation for anaphylaxis being made.

23.5 Japanese Encephalitis

Japanese encephalitis (JE) is a mosquito-borne infection caused by the eponymous *Flavivirus*. It is transmitted in an enzootic cycle between mosquitoes and vertebrate hosts, usually pigs and birds. This transmission is by *Culex* sp. mosquitoes, which are evening and night-time biting mosquitoes. The main *Culex* vector for JE is *Culex tritaeniorhynchus*, which commonly breed in flooded rice fields and ground pools, and so the greatest transmission is in rural agricultural areas of Asia where there are rice paddy fields and pig farms. Some urban transmission does occur.

The incubation period is around 15 days. Most infections are asymptomatic, but symptoms include fever, flu-like symptoms and headache. Signs of encephalitis, such as altered level of consciousness and convulsions, occur in approximately 1 in 300 infections and are more common in the paediatric population. Approximately 20–30% of symptomatic patients die, and of those that recover, 20–30% (21) are left with residual neurological problems including profound neurodisability, tremor, poor memory and psychological problems.

23.5.1 Epidemiology of JE in Travellers

JE was first described in Japan in the late 1800s, but it is now recognised throughout most of East and Southeast Asia, where it is a leading cause of viral encephalitis. China (excluding Taiwan) accounts for approximately 50% of cases. JE is also present in the Pacific Rim (see Image 23.3).

Recent estimates are that around 68,000 cases occur annually in endemic countries (an annual incidence of approximately 1.8 per 100,000 population). Seventy-five percent of cases occur in children (annual incidence of approximately 5.4 per 100,000 population) with a higher frequency in those over 3 years.

Peak transmission of the virus occurs between *May and September* for the temperate regions of Asia such as Korea and Japan; between *March and October* for the more tropical countries of Southeast Asia such as Thailand, Cambodia and Vietnam; *September to December* for Nepal and northern India; and *year round* in countries with year-round rainfall such as Malaysia, Indonesia and the Philippines.

The risk to most travellers to both Asia and the Pacific is very low with an estimated incidence of less than one case per million travellers. The risk is presumed to be highest

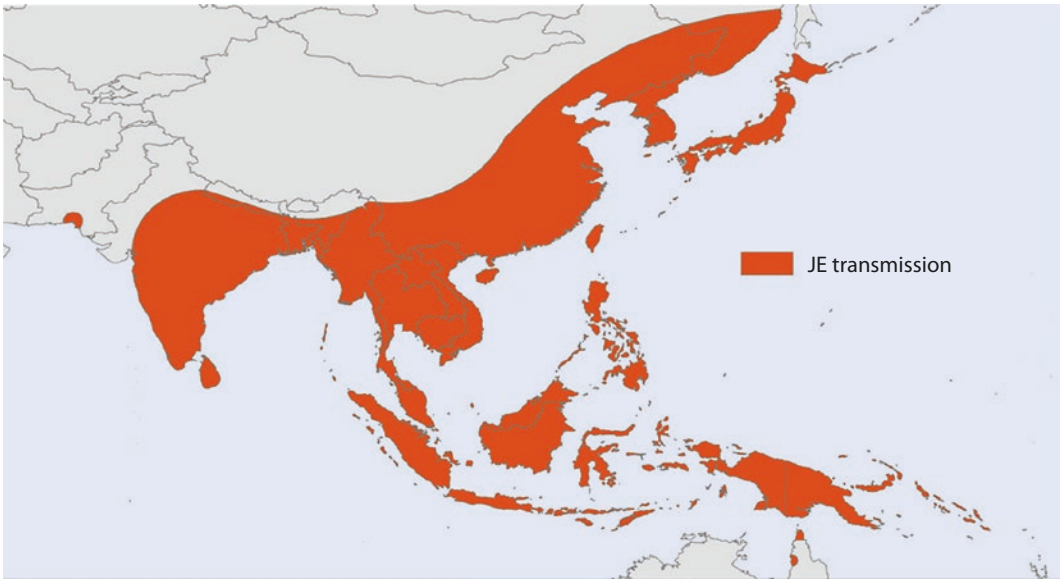


Image 23.3 The global distribution of JE. (*Source*: CDC ► https://www.cdc.gov/japaneseencephalitis/maps/index.html, ► http://apps.who.int/ithmap/)

for travellers staying in endemic areas for more than a few months, particularly during transmission seasons. The mainstay of prevention remains bite avoidance. There is no real indication to vaccinate the majority of travellers to East and Southeast Asia. Children travelling to endemic areas for long periods during the transmission season may be vaccinated.

23.5.2 JE Vaccination

The mouse brain–derived Beijing-1 and Nakayama strain vaccines (Green Cross Vaccine and JE-VAX®) are still used in some endemic countries but most are moving towards either the live attenuated recombinant vaccine (ChimeriVax-JE (IMOJEV®)) or the Vero cell–derived vaccine that is used in Europe.

Children from Australia or Southeast Asia may have received ChimeriVax-JE, which contains a live attenuated YFV-17D with the prM/E genes replaced with the corresponding JE virus SA14–142 strain genes. Whilst it is worth being aware that a child may have received a different formulation of vaccine overseas, IXIARO® by Valneva is the only JE vaccine licensed for paediatric administration in Europe.

IXIARO® contains the SA14–14-2 strain of JE virus, produced in Vero cells and inactivated. It is licenced from 2 months of age. The IXIARO® course consists of two doses given 1 month apart. The primary course should be completed at least 7 days before exposure. Children aged 2 months to 3 years receive 0.25 ml doses, and children aged above 3 years receive the adult doses of 0.5 ml. The manufacturer reports seroconversion in 85–100% of paediatric recipients at 6 months. No long-term seroprotection data has been generated for children, but adults demonstrate continued protection for up to 3 years. As such, a booster dose is recommended within the second year if continued protection is required.

There is no data on interrupted schedules in children, but Japanese encephalitis vaccine is highly immunogenic, and evidence from adults suggests that it is unnecessary to repeat the first dose after a schedule delay.

There was a relatively high risk of anaphylaxis with the mouse brain–derived JE vaccine and several contraindications, including that it was not to be used in children with neurological conditions. The Vero cell–derived, inactivated vaccine is usually well tolerated.

23.6 Cholera

Cholera is a bacterial disease caused by infection with toxigenic *Vibrio cholerae*. Cholera is acquired by consuming cholera-contaminated food or water, typically present in countries with poor sanitation and food hygiene, worldwide. Cholera outbreaks still occur in many low-income countries and particularly during humanitarian crises. Children in the 2–4-year age group are particularly affected.

The main features of cholera are the result of the release of cholera toxin, which binds to the intestinal cells and causes the efflux of ions and water into the bowel lumen that leads to watery diarrhoea. Only cholera serogroups 01 or 0139 produce toxin and thus cause epidemic disease. There are two biotypes of serogroup 01 – Classical and El Tor (which is further divided into Inaba, Ogawa and Hikojima).

Cholera is characterised by the sudden onset of profuse, watery stools with occasional vomiting. The incubation period is usually between 2 and 5 days but may be only a few hours. In severe cases, dehydration, metabolic acidosis and circulatory collapse may follow rapidly. Untreated, more than 50% of severe cases die within a few hours of onset. However, with prompt, correct treatment, mortality is less than 1%.

23.6.1 Cholera Vaccination

The mainstay of cholera prevention is food and water hygiene. Vaccination is rarely necessary for travellers. Children travelling to remote areas with epidemic cholera and limited access to basic medical care can be considered for vaccine.

Cholera is similar in structure to some strains of *E. coli*. The cholera vaccine also has limited protective effect against heat-labile enterotoxin-producing *E. coli*, one of the many causes of travellers' diarrhoea. The WC/rCBt oral vaccine is therefore licenced in some countries for preventing ETEC diarrhoea, but it should generally not be used for this purpose in travellers. The duration of its protection against ETEC is <3 months.

The licenced cholera vaccine in Europe is an inactivated oral vaccine named Dukoral® (Valneva).

The Dukoral® vaccine is licenced in Europe for children aged over 2 years.

The vaccine is supplied as granules, and a separate bicarbonate buffer suspension, which protects the vaccine from destruction by gastric acid. The primary course is two or three doses (depending on age) that must be drunk between 1 and 6 weeks apart. If more than 6 weeks elapse between the first two doses, the primary course should be restarted. All doses should be completed at least 1week before the exposure.

The vaccine contains recombinant cholera toxin B subunits plus the following strains of inactivated bacteria:

- *Vibrio cholerae* Inaba 01 classical biotype.
- *Vibrio cholerae* 01 Inaba El Tor biotype.
- *Vibrio cholerae* 01 Ogawa classical biotype.

As such it confers protection against serogroup 01 only. It does not protect against serogroup 0139 or any other vibrio species.

Since immunity is mediated by intestinal mucosal IgA, serological tests may not fully reflect immunity, but the reported protective efficacy against serogroup 01 cholera is around 68%, and it begins to wane quickly, after around 6 months (28). The wane is faster in infants. For continuous protection, therefore, a single booster dose is recommended 2 years after completing the primary course for children over 6 years of age, and 6 months after completing the primary course for children aged 2–6 years.

There are a number of other vaccines developed for immunisation against cholera, and most are oral. The least costly vaccine, used in endemic regions, is the bivalent 01 and 0139 whole-cell oral vaccine by Shanchol. This vaccine does not contain the cholera toxin B subunit and has an overall efficacy of about 52% during the first year and 62% in the second year, associated with minimal side effects.

23.6.2 Cholera Vaccine Side-Effect Profile and Contraindications

Mild gastrointestinal symptoms (abdominal pain, cramping, diarrhoea and nausea) are commonly reported adverse effects associated with oral cholera vaccine. Vaccine administration should be delayed in the event of an acute gastrointestinal or febrile illness.

The vaccine contains approximately 1.1 g of sodium per dose, and this can make it unsuitable for children with nephrotic syndrome or those who take a low-sodium diet for other medical reasons.

23.7 Typhoid

Salmonella typhi and *paratyphi* A/B/C are serotypes of the gram-negative bacteria *Salmonella enterica*. Travellers are infected by ingestion of contaminated food and water or by direct faeco-oral transmission in areas of poor sanitation.

The signs of enteric fever range from headache, myalgia, nausea and abdominal pain with constipation or diarrhoea to fever and sepsis with intestinal perforation and GI haemorrhage. Children may experience severe disease including meningitis and encephalopathy, presenting as seizures. Generally, severe disease (typhoid fever) is associated with *S. typhi* infection.

The majority of cases occur in Asia. In high-risk areas attack rates are up to 478/100,000 per annum in local school-age children and 358/100,000 annually in local 2–4-year-olds. The areas of highest incidence for travellers are India, Bangladesh and Pakistan. The disease is also endemic throughout Africa and South America but is rarely diagnosed in travellers from these two continents.

In travellers to the high typhoid-burden countries such as India, Bangladesh and Pakistan, the estimated infection rates are up to 10 per 100,000 travellers. Seventy-eight percent of those infections are in those who return to their birth countries to visit friends and relatives (VFRs). This highlights the importance of targeting children of VFR travellers in particular.

There is increasing antibiotic resistance in enteric fever cases in the endemic regions.

23.7.1 Typhoid Vaccination

Typhoid vaccination is often recommended for travellers to areas of South Asia. For low- and moderate-risk areas such as sub-Saharan Africa and South America, vaccination is not recommended.

The current licenced vaccines do not offer significant protection against *S. paratyphi*, and none of the licenced vaccines are suitable for infants and children under 2 years of age. All travellers should be advised on personal and food hygiene to help reduce infection risk.

23.7.2 Typhoid Vaccines

The inactivated whole-cell typhoid vaccine provided around 65–70% protection but caused strong adverse reactions, and its use has long been discontinued in Europe.

There is now a live oral vaccine, and two Vi capsular polysaccharide vaccines licenced for *Salmonella typhi*. They offer some protection but they have multiple shortcomings (Table 23.4).

The oral vaccines contain a live attenuated lyophilised TY21a strain that may be more immunogenic, particularly enhancing mucosal immunity. The oral vaccine administered with bicarbonate buffer in three doses over several days has an efficacy of up to 50% in the first 2 years after vaccination. Since oral TY21a is a live vaccine, it is avoided in immunocompromised children, and the use of any concomitant antibiotics will affect its efficacy.

Vi is the virulence factor and protective antigen in *Salmonella typhi*. The polysaccharide intramuscular vaccines are made of purified Vi polysaccharide from the Ty2 *Salmonella typhi* strain. They are single-dose vaccines.

Table 23.4 Typhoid vaccines currently in use

Vaccine type	Immunogenic constituents	Minimum age	Vaccine trade names	Number of doses in primary course	Duration of protection
Live attenuated oral vaccine	Live TY21a	6 years	Vivotif® (Crucell)	3	3 years (after 3 doses)
			Zerotyph (Boryung)	3	
Parenteral vaccine	Vi polysaccharide	2 years (unlicenced use between 1–2 years if benefit outweighs risk)	Typhim vi® (Sanofi Pasteur)	1	3 years
			Typherix® (GlaxoSmithKline)	1	

Neither elicits protective responses in children under 2, as expected for a polysaccharide vaccine in this age group. In older children it provides protection of approximately 60%. It is recommended for three yearly boosting, but anti-Vi IgG titres have been shown to decline well before that time period.

Vi conjugate vaccines are in development. One; Typbar-TCV a conjugate vaccine, coupled to tetanus toxoid, has been used in India. It was found to have a protective efficacy of 89% against the typhoid triad (fever ≥38.0 °C, headache and abdominal pain). Other conjugate vaccines, Vi-CRM 197 and Vi-rEPA have demonstrated significant immunogenicity, good safety profiles and protective efficacies of around 89%. This new generation of typhoid conjugate vaccines may provide practitioners with a vaccine that is suitable for travellers, particularly for the high-risk group of preschool children but are yet to be registered in Europe and North America.

23.8 Vaccines with No Current Indications for Travellers

23.8.1 Dengue

Dengue is one of the worlds' most common infectious diseases, endemic to more than 110 countries (see Image 23.4). The dengue virus, which belongs to the *Flaviviridae* family, is the etiologic agent responsible for the broad spectrum of dengue symptoms and signs that range from mild fever (DF) to dengue haemorrhagic fever and dengue shock syndrome.

There are four dengue serotypes, DEN-1, DEN-2, DEN-3 and DEN-4, and any useful vaccine would need to provide protection to all four serotypes. Previous concerns regarding antibody-dependent enhancement effects and activity of cross-reactive T cells during repeat dengue infection have somewhat slowed the development of a safe and effective dengue vaccine.

Each dengue virus is a single-stranded RNA virus that encodes three structural proteins (capsid protein C, pre-membrane protein (prM) and envelope protein E), plus seven non-structural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5). The envelope protein (protein E) has the main epitopes for the production of neutralising antibody and was therefore considered the best target for vaccine development.

23.8.2 Epidemiology of Dengue in Travellers

Dengue is the commonest disease contracted by travellers to SE Asia aside from Travellers' diarrhoea.

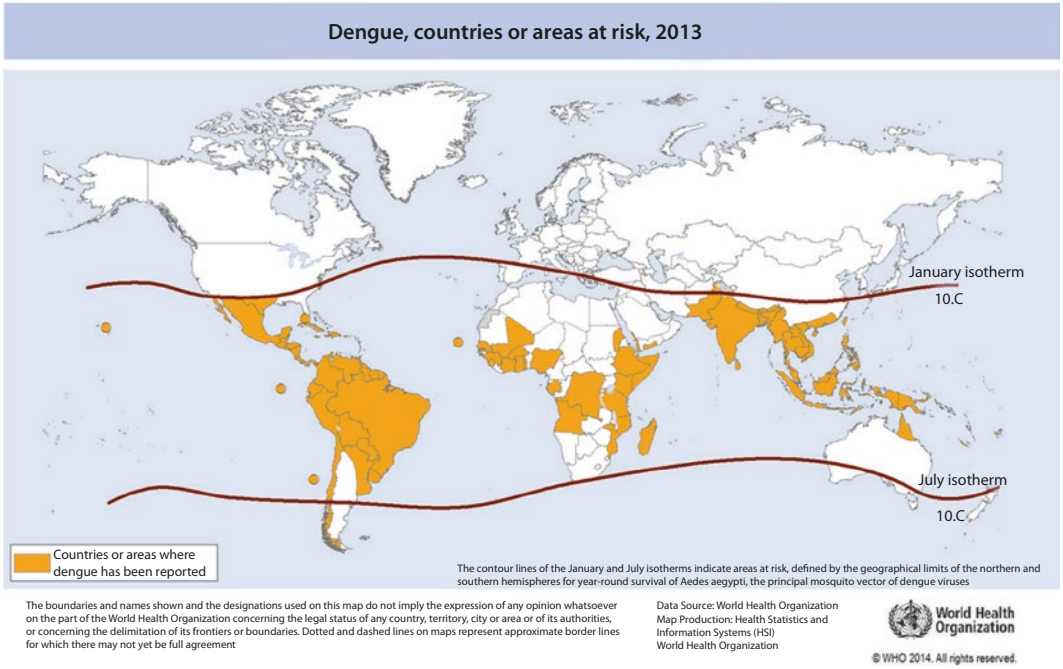


Image 23.4 Global distribution of dengue. (*Source*: WHO ► http://apps.who.int/ithmap/)

23.8.3 Dengue Vaccines

Dengvaxia®, a live, attenuated, tetravalent vaccine developed by Sanofi Pasteur, is the first licenced vaccine for dengue prevention. Dengvaxia is based on a genetically engineered live attenuated YF virus, whereby the prM and E genes from each of the four dengue serotypes are substituted into the backbone of the yellow fever virus, 17D vaccine strain. It is available in several endemic countries where dengue is a leading cause of child mortality.

Two large phase III efficacy trials conducted in endemic areas of Latin America and Asia showed the efficacy of the vaccine to vary from 77.7% for serotype 4, 74.0% for serotypes 2 and 3 to 42.3% for serotype 1. In the Pacific region, the overall efficacy is just 56.5%, with the greatest impact being in the prevention of severe dengue and hospitalisation. In previously unexposed children, the vaccine efficacy is only 38%. It has been proposed that this is due to the lack of non-structural (NS1–5) dengue virus proteins in the vaccine. Sadly, a long-term follow-up study of children between 2 and 16 years of age in the Asia-Pacific and Latin American regions demonstrated increased morbidity and hospitalisations for severe dengue (antibody-dependent enhanced disease) among children under 9 years, and fuelled anti-vaccine campaigns.

Dengvaxia® is now licenced in 19 countries only for children who have laboratory evidence of previous dengue exposure, for example Dengue IgG ELISA. It is a three-dose schedule with doses 6 months apart.

Five other dengue vaccine candidates are in clinical trials, and multiple strategies have been exploited for vaccine development. Tetravalent inactivated vaccines appear to be safer. Two of these entered phase III clinical trials in 2019. A phase III double-blind RCT of a tetravalent dengue vaccine by Japanese company TAKEDA published promising data in 2020. This study randomised over 20,000 healthy children from endemic regions across Latin America and Asia to two doses of TAK3 vaccine or placebo 3 months apart and found overall vaccine efficacy of 80% at 11 months using RT PCR tests. The efficacy

varied by subtype but prevented hospitalisation in up to 90%. Importantly serostatus prior to vaccination was assessed on entry to the study so as to monitor for antibody-dependent enhancement and more severe clinical outcomes in the longer term of vaccine recipients.

The NS1 surface protein is another potential vaccine candidate. Passive immunisation with anti-NS1 antibodies prevented lethal dengue disease in a mouse model. As such, several strategies for NS1-based vaccines are under investigation.

23.8.4 Zika

Zika virus (ZIKV) is a flavivirus spread by *Aedes aegypti*. First described in Zika, Uganda, it has an Asian and African lineage but one serotype. It is now widespread across Oceania, Africa, South Asia, North, Central and South America. More than two-thirds of travel-associated cases in Europe are associated with travel to the Caribbean.

Zika is particularly familiar to paediatricians due to its association with cerebral atrophy and neonatal microcephaly, for which it was declared a Public Health Emergency of International Concern (PHEIC) in 2016. Zika in pregnant women can lead to these congenital effects, now named Congenital Zika Syndrome. Zika in children causes similar symptoms to those of adults; fever, myalgia, headache, arthralgia and maculopapular rash. The rash is highly pruritic and may be associated with oedema of hands and feet. In more severe cases joint swelling and neurological sequelae such as Guillain-Barre, acute myelitis, posterior uveitis and hearing loss may occur.

Zika is high priority for vaccine development, and a vaccine roadmap has been developed by WHO. There are currently a number of phase I preclinical vaccine trials both for DNA and inactivated whole-cell vaccines. The most advanced to date is a phase II trial vaccine which uses plasmid-based DNA encoding for the E and prM proteins (animal studies found these to be highly immunogenic). This study enrolled 2338 participants and completed in late 2019 but has yet to be published by the US NIAID.

23.8.5 Malaria

Malaria is present in Africa, South East Asia and the Mediterranean. Over 90% of cases are in sub-Saharan Africa, where it causes over 450,000 deaths per annum. *Plasmodium falciparum* accounts for more than 90% of these deaths.

Severe malaria, and its associated mortality, peaks in the under-fives, particularly the under-twos. Infants and children in Africa typically suffer multiple episodes of severe clinical malaria before developing a degree of immunity. It is unclear whether immunity ever occurs in adults, as opposed to immune tolerance.

Studies support that liver-resident $CD8^+$ T cells are likely the primary mediators of any long-term immunity. Non-recirculating liver resident $CD8^+$ T cells play a critical role in protection but clearly cannot be assessed in human trials. Antibodies and $CD4^+$ T cells are also elicited after immunisation and are used to define immunity in human studies. Antibodies to antigens present on malaria sporozoites such as the circumsporozoite protein (CSP) have been shown to prevent sporozoites migrating to liver cells, and thus a vaccine targeted to CSP could theoretically stop a pre-erythrocytic infection from developing in the liver. Alternatively merozoite surface antigens or gametocyte surface antigens could be targeted to reduce multiplication in the blood stage. Combination vaccines acting on more than one stage of the parasites life cycle could induce broader immune responses.

A vaccine is needed primarily for the use in children living in endemic countries, although a vaccine would clearly be useful for paediatric travellers to those countries.

23.8.6 Malaria Vaccines

There are currently more than 30 malaria vaccines in preclinical or clinical trials and we

discuss two vaccines, one of which is licenced and the other shows a mechanism for complete protection.

RTS,S/ASO1 Vaccine

RTS,S/AS01 (Mosquirix®) is the WHO-approved malaria vaccine. It has been developed by GSK and collaborators, within a public–private partnership, to produce a vaccine for African children.

RTS,S acts on the pre-erythrocytic stage of malaria. It is a recombinant hybrid where portions of the CSP protein are fused to hepatitis B surface antigen and co-expressed in yeast. RTS,S virus-like particles are formed when the fusion protein is expressed within yeast cells. ASO1 is the adjuvant, made of immune-modulatory molecules and liposomes. The vaccine is given by IM injection and has been evaluated in trials using a 0-, 1-, 2-month schedule, with a booster 18 months after the third dose.

Clinical trials have demonstrated safety and immunogenicity. They also importantly demonstrated non-inferiority of hepatitis B immunity compared to Engerix-B vaccination and no deleterious effect on other co-administered vaccines responses. A double-blind, randomised controlled trial, conducted in seven African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and Tanzania) from 2009 to 2011, showed that the three-dose primary schedule of RTS,S reduced clinical malaria cases by 28% in children and 18% in infants, over at least 3 years after vaccination. A booster dose of RTS,S administered 18 months after the primary schedule further reduced the number of cases of clinical malaria in children (aged 5–17 months at first vaccination) by 36% and in infants (aged 6–12 weeks at first vaccination) by 26% to the end of the study, with average follow-up of 48 and 38 months, respectively.

Although very promising, it is important to note that this was tested in a population of whom 80% used insecticide-treated bed nets, and that protection decreased over time in both age groups. There was also an increased risk of severe malaria and malaria mortality and a significant disproportionate increase in overall mortality in children who did not receive the booster dose. This led to concern that the RTS,S/AS01 vaccination may prevent the normal development of malaria immunity, and malaria interventions in young children might lead to rebound morbidity and mortality in older age groups.

The European Medicines Agency gave a positive scientific opinion for RTS,S, and vaccine immunisation programmes started in 2019 in 3 sub-Saharan African countries, but the vaccine is not being studied in travellers at present. The question of whether children who received a malaria vaccine would be at higher risk after a period of non-exposure, or without boosters, than malaria-naïve children is still unanswered. It is unlikely ever to be used in travellers, as the efficacy would be suboptimal.

Whole Sporozoite Vaccine (WSV)

Vaccines against the whole malaria sporozoite have produced immunity from 35% to 100%, depending on prior exposure. They are more immunogenic in malaria-naïve individuals. Whole sporozoite vaccines (WSV) in development include radiation attenuated or genetically attenuated sporozoites, and sporozoites administered under drug cover, the so-called ‘Infection treatment vaccination’.

The infecting dose required is small (~6 sporozoites), yet the sporozoite is a complex organism that develops in the mosquito, and the in vitro production of the sporozoite for the use as antigen has yet to be achieved. Therefore, these vaccines require sporozoites to be dissected out of mosquitoes which is a technically difficult and time-consuming process. This is a significant hurdle to the manufacturing process.

A randomised controlled trial of a chemo-attenuated plasmodium falciparum sporozoite (PfSPZ) vaccine was published in 2017. It was tested on nine malaria-naïve adult participants. These participants received three doses of 5.12×10^4 PfSPZ by IV injection at 4-weekly intervals whilst taking chloroquine antimalarial prophylaxis. At this dose it prevented 100% of infections when these nine participants underwent controlled malaria

infection 10 weeks later. The vaccine appears safe yet is impractical for large-scale cost-effective vaccination.

Immunisation studies involving different routes of vaccine administration find the greatest protection comes from IV vaccination rather than IM or intradermal and all current methods in trial involve delivery by mosquito bite or by IV injection.

We propose that while the costs may be prohibitory for short-stay travellers, it could be available for long-term expatriate, malaria-naïve travellers in future if larger studies replicate these excellent results.

23.8.7 SARS-CoV-2 Vaccines (See ◘ Chap. 26)

The development of vaccines against COVID-19 disease is the main focus of scientists across the globe at this time. In the context of travelling populations, including paediatric populations, these will have a critical role. It is likely that all travellers in the future will need to provide, on entering travel destinations, evidence of immunity or vaccination against COVID-19. It is important therefore that in any future vaccination campaign, children are fully immunised so as to facilitate family travel. It will be necessary for this and other purposes, that COVID-19 vaccines be evaluated in paediatric populations to confirm safety and efficacy.

Further Reading

Bhutta Z, et al. Immunogenicity and safety of the vi-CRM197 conjugate vaccine against typhoid fever in adults, children, and infants in south and southeast Asia: results from two randomised, observer-blind, age de-escalation, phase 2 trials. Lancet Infect Dis. 2014;14(2):119–29.

Biswal S, Borja-Tabora C, Martinez Vargas L, Velásquez H, Theresa Alera M, Sierra V, Johana Rodriguez-Arenales E, Yu D, Wickramasinghe VP, Duarte Moreira E Jr., Fernando AD, Gunasekera D, Kosalaraksa P, Espinoza F, López-Medina E, Bravo L, Tuboi S, Hutagalung Y, Garbes P, Escudero I, Rauscher M, Bizjajeva S, LeFevre I, Borkowski A, Saez-Llorens X, Wallace D; TIDES study group. Efficacy of a tetravalent dengue vaccine in healthy children aged 4–16 years: a randomised, placebo-controlled, phase 3 trial. Lancet. 2020 May 2;395(10234):1423–1433. doi: https://doi.org/10.1016/S0140-6736(20)30414-1. Epub 2020 Mar 17. Erratum in: Lancet. 2020 Apr 4;395(10230):1114.

Casey, M., Harris, J.B., Hyde, T.B. et al. Immunogenicity of Fractional-Dose Vaccine during a Yellow Fever Outbreak — Final Report Rebecca N Engl J Med 2019; 381:444–454.

CDC. Grading of recommendations, assessment, development, and evaluation (GRADE) for yellow fever vaccine booster doses. Advisory Committee on Immunization Practices. CDC. 2015.

de Menezes MR, Fernandes Leal Mda L, Homma A. Serious adverse events associated with yellow fever vaccine. Hum Vaccin Immunother. 2015;11(9):2183–7.

Gautret P, Parola P. Rabies vaccination in travelers: a global perspective. J Travel Med. 2012;19(6):395–6.

Gautret P, Shaw M, Gazin P, Soula G, Delmont J, Parola P, et al. Rabies postexposure prophylaxis in returned injured travelers from France, Australia, and New Zealand: a retrospective study. J Travel Med. 2008;15(1):25–30.

Gossner Céline M, Haussig Joana M , de Bellegarde de Saint Lary Chiara , Kaasik Aaslav Kaja , Schlagenhauf Patricia , Sudre Bertrand . Increased risk of yellow fever infections among unvaccinated European travellers due to ongoing outbreak in Brazil, July 2017 to March 2018. Euro Surveill. 2018;23(11):pii=18–00106. https://doi.org/10.2807/1560-7917.ES.2018.23.11.18-00106

Gotuzzo E, Yactayo S, Cordova E. Efficacy and duration of immunity after yellow fever vaccination: systematic review on the need for a booster every 10 years. Am J Trop Med Hyg. 2013;89(3):434–44.

Hills SL, Griggs AC, Fischer M. Japanese encephalitis in travelers from non-endemic countries, 1973-2008. Am J Trop Med Hyg. 2010;82(5):930–6.

Japanese Encephalitis Vaccines: WHO position paper – February 2015. WHO; February 2015.

Kossaczka Z, Lin FY, Ho VA, NTT T, Bay PV, Thanh TC, et al. Safety and immunogenicity of vi conjugate vaccines for typhoid fever in adults, teenagers, and 2- to 4-year-old children in Vietnam. Infect Immun. 1999;67(11):5806–10.

Liu Y, Liu J, Cheng G. Vaccines and immunization strategies for dengue prevention. Emerg Microbes Infect. 2016;5(7):e77.

Malerczyk C, Vakil HB, Bender W. Rabies pre-exposure vaccination of children with purified chick embryo cell vaccine (PCECV). Hum Vaccin Immunother. 2013;9(7):1454–9.

Monath TP. Review of the risks and benefits of yellow fever vaccination including some new analyses. Expert Rev. Vaccines. 2012;11(4):427–48.

Morbidity and Mortality Weekly Report: Human Rabies Prevention – United States, 2008. Recommendations of the Advisory Committee on Immunization Practices [press release]. CDC: 2008.

Mordmüller B, Surat G, Lagler H, Chakravarty S, Ishizuka AS, Lalremruata A, Gmeiner M, Campo JJ, Esen M, Ruben AJ, Held J, Calle CL, Mengue JB, Gebru T, Ibáñez J, Sulyok M, James ER, Billingsley PF, Natasha KC, Manoj A, Murshedkar T, Gunasekera A, Eappen AG, Li T, Stafford RE, Li M, Felgner PL, Seder RA, Richie TL, Sim BK, Hoffman SL, Kremsner PG. Sterile protection against human malaria by chemoattenuated PfSPZ vaccine. Nature. 2017 Feb 23;542(7642):445-449. doi: https://doi.org/10.1038/nature21060. Epub 2017 Feb 15.

Roukens AH, Vossen AC, van Dissel JT, Visser LG. Reduced intradermal test dose of yellow fever vaccine induces protective immunity in individuals with egg allergy. Vaccine. 2009;27(18):2408–9.

RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet. 2015;368(9988):31–45.

Seder RA, et al. Protection against malaria by intravenous immunization with a nonreplicating sporozoite vaccine. Science. 2013;341(6152):1359–65.

Shlim DR, Solomon T, Ericsson CD, Steffen R. Japanese encephalitis vaccine for travelers: exploring the limits of risk. Clin Infect Dis. 2002;35(2):183–8.

Staples, E.J, Barrett, A.D.T. Wilder-Smith, A. and Hombach, J. (2020) Review of data and knowledge gaps regarding yellow fever vaccine-induced immunity and duration of protection. *Vaccines* **5**:1

Steinberg EB, Bishop R, Haber P, Dempsey F, Hoekstra M, Nelson JM, et al. Typhoid fever in travelers: who should be targeted for prevention? Clin Infect Dis. 2004;39:186–91.

Sur D, et al. Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial. Lancet. 2009;374(9702):1694–702.

Szu S. Development of vi conjugate – a new generation of typhoid vaccine. Expert Rev. Vaccines. 2013;12(11):1273–86.

Traiber C, Coelho-Amaral P, Ritter VR, Winge A. Infant meningoencephalitis caused by yellow fever vaccine virus transmitted via breastmilk. J Pediatr (Rio J) 2011;87:269–72.

WHO. World Health Organisation, Rabies Fact Sheet. http://www.who.int/rabies/en/. WHO; 2014 (updated 2016).

Winge A, Ritter V, Coelho-Amaral P, Traiber C. Infant meningoencephalitis probably caused by yellow fever vaccine virus transmitted via breastmilk. J Pediatr. 2011;87(3):269–72.

New Vaccines in Pipeline Development

Contents

GBS and CMV Vaccines in Pipeline Development

Christine E. Jones, Paul T. Heath, and Kirsty Le Doare

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_24

24

24.1 Group B Streptococcus Vaccines

24.1.1 Burden of Disease

Group B streptococcus (GBS) is well recognized as a cause of early neonatal infection in high-income countries (HICs), with long-term adverse neurodevelopmental outcomes in up to 50% of survivors of GBS meningitis. A global meta-analysis in 2015 estimated 205,000 infants with early-onset disease and 114,000 with late-onset disease per annum, with 90,000 deaths in infants <3 months age, and at least 10,000 children with disability each year. Up to 3.5 million preterm births may be attributable to GBS. Africa accounted for 54% of estimated cases and 65% of all fetal/infant deaths.

Many HICs have introduced intrapartum antibiotic prophylaxis (IAP) strategies in order to reduce the burden of neonatal early-onset GBS disease (EOD, disease within the first 7 days of life). Since the introduction of IAP policies in the USA, rates of EOD have declined from 1.7 per 1000 live births in the 1990s to 0.34–0.37 per 1000 live births in 2014. However, late-onset GBS disease (LOD, disease between 7 and 90 days of life) is not affected by IAP and has not declined; in the USA, the rate of GBS LOD has now overtaken that of EOD.

24.1.2 Epidemiology

GBS can colonize the vagina and gastrointestinal tract of pregnant women and be transmitted vertically to their babies during delivery. Up to 30% of women carry GBS in the vagina or rectum without it causing symptoms. Vertical transmission occurs in 15–50% of infants born to colonized mothers. Although the majority of such babies will not go on to develop invasive disease, maternal colonization is a prerequisite for EOD and a significant risk factor for LOD. Overall, EOD accounts for approximately 60–70% of all neonatal GBS disease, depending on the use of IAP in the population. LOD also results from vertical transmission from a colonized mother, but nosocomial transmission, breast milk, and community sources are also recognized.

24.1.3 GBS Vaccines

Given the very early onset of neonatal GBS disease and the shortcomings of IAP-based prevention strategies, there is considerable interest in developing an effective antenatal vaccine. The majority of work in this field over the last 30 years has focused on the development of a vaccine based on capsular polysaccharide (CPS), in part reflecting the success of this approach for other encapsulated bacteria such as *Streptococcus pneumoniae*, but also by the demonstration, initially by Baker et al. in 1976, of the association between GBS serotype-specific capsular antibody concentrations and invasive GBS disease in newborns. In the USA and Europe, GBS serotypes causing invasive disease are predominantly Ia, Ib, II, III, IV, and V.

CPS–protein conjugate vaccines against all relevant serotypes have been assessed in healthy, nonpregnant women and demonstrated satisfactory immunogenicity and safety. More recently, conjugate vaccines have been developed based on tetanus toxoid and CRM197 as the carrier proteins. Studies in pregnant women have also established the immunogenicity and safety of these candidates. A study of a trivalent CRM-conjugate vaccine involving 470 pregnant women demonstrated a satisfactory reactogenicity profile, immunogenicity, and antibody transfer to the infant. A hexavalent conjugate vaccine (GBS6) has now been tested in healthy nonpregnant women and found to be safe and immunogenic. Vaccine trials in pregnant women are currently underway in South Africa (► ClinicalTrials.gov Identifier: NCT03765073). Two manufacturers, BioVac in South Africa and Inventprice in the USA, are also in the preclinical development stage for multivalent vaccines.

The use of CPS conjugate vaccines is not without its drawbacks, including cost, limited strain coverage, and, potentially, serotype replacement. One way of overcom-

ing these limitations is to develop a vaccine based on highly conserved surface proteins. A phase I trial of a protein vaccine incorporating Rib and Alpha C surface proteins has recently completed and results are awaited (► Clinicaltrials.gov: NCT02459262). The use of "reverse vaccinology" has also identified four proteins that could be the basis of a "universal" vaccine: the pilus proteins and the Sip protein.

Several obstacles exist in moving the most advanced vaccine into phase III clinical trials. Given the relative rarity of GBS disease in Europe and the USA, large numbers of infants would need to be recruited to determine vaccine efficacy. Efficacy trials are likely to be needed because it is not currently known what concentration of antibody is required to protect infants. However, generation of robust data supporting serological correlates of protection could facilitate the licensure of a GBS vaccine without the need for large-scale prelicensure efficacy trials in pregnant women.

24.2 Cytomegalovirus (CMV)

24.2.1 CMV Vaccines

Cytomegalovirus (CMV) is the most common cause of congenital infection globally and can be associated with significant sequelae in affected infants. Congenital CMV infection is the leading nongenetic cause of sensorineural hearing loss (SNHL), the only potentially treatable cause, and is associated with neurodevelopmental delay.

CMV infection is usually asymptomatic or associated with mild, transient symptoms in immunocompetent children and adults; however, in immunocompromised individuals, primary or reactivated virus can cause substantial morbidity.

Transmission of CMV to the fetus can occur following primary maternal infection, reactivation, or reinfection with a different strain. The rate of transmission to infants born to women with primary CMV infection is substantially higher, 32%, compared to those infants born to women with reactivation, 1.4%. The global birth prevalence of congenital cytomegalovirus (cCMV) is 0.64%, with significant variation between countries. The total prevalence represents the sum of transmission following primary infection and reactivation during pregnancy.

Around 10–15% of congenitally infected infants (cCMV) will have symptoms at birth. Clinical features of cCMV seen in the majority (>50%) of symptomatic infants include petechiae, jaundice, hepatosplenomegaly, microcephaly, intrauterine growth retardation, elevated ALT, and low platelets. Features observed less frequently include chorioretinitis, optic atrophy, purpura, and seizures. The most common finding on neuroimaging is intracranial calcification, with some infants also demonstrating ventricular dilatation, cysts, and lenticulostriate vasculopathy. A high proportion of symptomatic infants (40–60%) will experience adverse neurodevelopmental outcomes, such as cerebral palsy, cognitive impairment, and SNHL.

About 10–15% of infants with cCMV who are not symptomatic at birth will still develop SNHL, which in some is progressive.

Prevention of congenital CMV (cCMV) infection is a major driver of CMV vaccine development.

24.2.2 Vaccines

CMV vaccine development has a relatively long history, starting in the 1970s with live-attenuated vaccines. The live-attenuated CMV vaccines were associated with only mild injection-site reactions and no systemic reactions and induced antibodies at similar concentrations to natural infection, and no excretion of virus was detected. The laboratory strains of CMV lost the ULb′ region of the genome during the multiple cell culture passages, therefore losing genes permitting entry into epithelial cells. Therefore, these vaccines did not elicit the high concentrations of antibody needed to prevent viral entry into cells, and a clinical trial of women with young children attending childcare facilities showed that vaccination did not prevent primary or secondary infection.

In the 1980s and 1990s, recombinant subunit vaccines incorporating CMV surface glycoprotein B (gB), adjuvanted with MF59, were first developed and tested. The vaccine-induced gB antibody is thought to be important for prevention of viral entry into fibroblasts. The vaccine was well tolerated and immunogenic, more so in infants than in adults, and induced antibody responses of higher magnitude than natural infection; however, immunity quickly waned. The protection afforded to adolescent girls was at best modest, up to 45%. Similar results were also observed in CMV seronegative women with vaccine efficacy of 50%.

Other candidates in the vaccine pipeline include CMV DNA vaccines that contain both gB and pp65, another surface protein. The pp65 protein is an abundant protein in CMV virions and is a major target of the T-cell responses to CMV. One such vaccine, CyMVectin, was in late preclinical development, but has since been withdrawn.

More recently, there has been interest in vaccines containing more immunogens. CMV has a pentameric gH/gL/UL128-UL130-UL131 complex on its surface that is critical to viral entry and is an important target of the neutralizing antibody response in seropositive individuals. An association between antibodies to this pentamer and prevention of transmission of primary CMV from mother to fetus has been demonstrated.

Whole-virus CMV vaccines are again being explored, based on the AD169 strain, however with the restoration of the expression of the pentamer and with an elegant inbuilt genetic mechanism that enables tight regulation of viral replication. Replication can only occur in the presence of a synthetic compound (not found in nature) called Shield-1. When this is provided viral stocks of the vaccine V160 can be grown, but it is unable to replicate in the host. Phase I studies have been completed and phase IIb will commence in the near future.

A messenger RNA (mRNA)-based vaccine encoding target antigens (pentamer complex and gB) presents a new approach to CMV vaccines. The mRNA is translated into proteins within the host cell and then the immune system is able to recognize these antigens and produce an immune response. A phase I randomized placebo-controlled dose-ranging study has recently been completed (► clinicaltrials.gov identifier: NCT03382405) evaluating the safety and immunogenicity of mRNA-1647 and mRNA-1443. A subsequent phase II dose-confirming study of mRNA-1647 using the final product in a lyophilized formulation (► Clinicaltrials.gov identifier: NCT04232280) is ongoing. Large-scale phase III clinical trials are soon to commence in women of childbearing age to evaluate the efficacy of mRNA-1647 in preventing primary CMV infection. These studies represent a step-change in the development of a vaccine against CMV. The first-ever mRNA vaccines have recently received conditional approval for the prevention of SARS-CoV-2 and one of these is by the same vaccine manufacturer (Moderna) as the CMV mRNA vaccine; this provides confidence that this approach is safe and renewed hope for a CMV vaccine candidate that will have clinical efficacy.

24.2.3 Other Issues

The immune correlates of protection against cCMV have not fully been elucidated, including the contribution of humoral and cellular immunity to maternal–fetal transmission. Determining relevant endpoints in clinical trials to support vaccine licensure is critical, given that immune correlates remain elusive and clinical endpoints are required, such as cCMV infection. Such trials necessitate very large sample sizes and long follow-up to achieve sufficient statistical power and are costly. Optimizing the protective efficacy of CMV vaccines in both seronegative and seropositive individuals is critical, since a significant number of infants with cCMV are born to women with preexisting CMV antibody.

A further significant issue is the timing of vaccination. A vaccine should ideally be administered prior to pregnancy to ensure immunity before the first trimester; however, many pregnancies are not planned, and

women do not necessarily seek preconception healthcare. Vaccinating adolescents is an alternative; however, persistence of immunity into reproductive years may be challenging, and a vaccine would need to be effective in both seronegative and seropositive females. Another possibility is to vaccinate in early childhood. Vaccinating as part of the routine infant immunization program would ensure high coverage; could prevent infection prior to first encounter, thereby overcoming the problems of immunity in seropositive individuals; and would interrupt viral circulation by preventing prolonged shedding of CMV in the urine and saliva of infected toddlers. This age group is the most common source of infection to pregnant women and therefore would afford protection to the mothers or caregivers of young children. Modelling suggests that a combination strategy may be preferable.

Further Reading

Absalon J, Segall N, Block SN et al safety and immunogenicity of a novel hexavalent group B streptococcus conjugate vaccine in healthy, non-pregnant adults: a phase 1/2, randomised, placebo-controlled, observer-blinded, dose-escalation trial. Lancet Infect Dis. 2020;21(2):263−274

Adler SP, Starr SE, Plotkin SA, Hempfling SH, Buis J, Lou Manning M, et al. Immunity induced by primary human cytomegalovirus infection protects against secondary infection among women of childbearing age. J Infect Dis 1995;171:26–32. doi: https://doi.org/10.1093/infdis/171.1.26.

Baker CJ, Kasper DL. Correlation of maternal antibody deficiency with susceptibility to neonatal group B streptococcal infection. N Engl J Med 1976;294(14):753–6.

Baker CJ, Rench MA, McInnes P. Immunization of pregnant women with group B streptococcal type III capsular polysaccharide-tetanus toxoid conjugate vaccine. Vaccine 2003;21(24):3468–72.

Bernstein DI, Munoz FM, Callahan ST, Rupp R, Wootton SH, Edwards KM, et al. Safety and efficacy of a cytomegalovirus glycoprotein B (gB) vaccine in adolescent girls: a randomized clinical trial. Vaccine 2016;34:313–9. doi: https://doi.org/10.1016/j.vaccine.2015.11.056

Brodeur BR, Boyer M, Charlebois I, Hamel J, Couture F, Rioux CR, et al. Identification of group B streptococcal sip protein, which elicits cross-protective immunity. Infect Immun 2000;68(10):5610–8.

Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. Rev Med Virol 2007;17:355–63. doi: https://doi.org/10.1002/rmv.544.

Fouts AE, Chan P, Stephan JP, Vandlen R, Feierbach B. Antibodies against the gH/gL/UL128/UL130/UL131 complex comprise the majority of the anti-cytomegalovirus (anti-CMV) neutralizing antibody response in CMV hyperimmune globulin. J Virol 2012;86:7444–7. doi: https://doi.org/10.1128/JVI.00467-12.

Heath PT, Schuchat A. Perinatal group B streptococcal disease. Best Pract Res Clin Obstet Gynaecol 2007;21(3):411–24.

Heyderman RS, Madhi SA, French N, Cutland C, Ngwira B, Kayambo D, et al. Group B streptococcus vaccination in pregnant women with or without HIV in Africa: a non-randomised phase 2, open-label, multicentre trial. Lancet Infect Dis 2016;16(5):546–55.

John, S., Yuzhakov, O., Woods, A., Deterling, J., Hassett, K., Shaw, C. A., & Ciaramella, G. (2018). Multi-antigenic human cytomegalovirus mRNA vaccines that elicit potent humoral and cell-mediated immunity. Vaccine, 36(12), 1689–1699. https://doi.org/10.1016/j.vaccine.2018.01.029

Lanzieri TM, Bialek SR, Ortega-Sanchez IR, Gambhir M. Modeling the potential impact of vaccination on the epidemiology of congenital cytomegalovirus infection. Vaccine. 2014;32:3780–6. doi: https://doi.org/10.1016/j.vaccine.2014.05.014.

Le Doare K, Heath PT. An overview of global GBS epidemiology. Vaccine 2013;31(Suppl 4):D7–12.

Lilleri D, Kabanova A, Revello MG, Percivalle E, Sarasini A, Genini E, et al. Fetal human cytomegalovirus transmission correlates with delayed maternal antibodies to gH/gL/pUL128-130-131 complex during primary infection. PLoS One 2013;8:e59863–13. doi: https://doi.org/10.1371/journal.pone.0059863.

Liu, Y., Freed, D. C., Li, L., Tang, A., Li, F., Murray, E. M., et al. (2019). A Replication-Defective Human Cytomegalovirus Vaccine Elicits Humoral Immune Responses Analogous to Those with Natural Infection. J Virol, 93(23):e00747-19. https://doi.org/10.1128/JVI.00747-19

Maione D, Margarit I, Rinaudo CD, Masignani V, Mora M, Scarselli M, et al. Identification of a universal group B streptococcus vaccine by multiple genome screen. Science 2005;309(5731):148–50.

Margarit I, Rinaudo CD, Galeotti CL, Maione D, Ghezzo C, Buttazzoni E, et al. Preventing bacterial infections with pilus-based vaccines: the group B streptococcus paradigm. J Infect Dis 2009;199(1):108–15.

Neostrep. Neostrep – development of group B streptococcal vaccine. 2016 [cited 2016.24/01/16]; Available from: http://www.neostrep.eu/index.html

Pass RF, Zhang C, Evans A, Simpson T, Andrews W, Huang M-L, et al. Vaccine prevention of mater-

nal cytomegalovirus infection. N Engl J Med 2009;360:1191–9. doi: https://doi.org/10.1056/NEJMoa0804749.

Plotkin S. The history of vaccination against cytomegalovirus. Med Microbiol Immunol 2015;204:247–54. doi: https://doi.org/10.1007/s00430-015-0388-z.

Seale A, Bianchi-Jassir F, Russell NJ et al. Estimates of the Burden of Group B Streptococcal Disease Worldwide for Pregnant Women, Stillbirths, and Children; Clin Infect Dis. 2017;65(suppl_2): S200-S219

Schrag SJ, Verani JR. Intrapartum antibiotic prophylaxis for the prevention of perinatal group B streptococcal disease: experience in the United States and implications for a potential group B streptococcal vaccine. Vaccine 2013;31(Suppl 4):D20–6.

Norovirus Vaccines in Pipeline Development

Timo Vesikari

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_25

25

25.1 Noroviruses and the Disease

Noroviruses (NoVs) are, after rotaviruses (RV), the second most common causative agents of acute gastroenteritis (GE) in young children. Globally, NoV GE carries significant mortality in children under 5 years of age; one estimate puts the annual death toll at 50,000, which is about one-third of that associated with rotavirus (see Chap. 11). In industrialized countries, deaths in children are rare, but there is significant mortality from NoV GE in the elderly. The yearly financial burden of Nov is estimated at 60 billion US dollars. Therefore, NoV vaccine development is targeted at both children and adults, often with greater emphasis on the latter. In industrialized countries, the burden of NoV disease in children, as measured by severe cases seen in hospital, was about one-third to one-half of that of RV disease before vaccinations.

Noroviruses were discovered in 1972 by A. Z. Kapikian of National Institutes of Health (NIH) using electron microscopy on stool samples collected from a 1968 outbreak in Norwalk, Ohio. The new virus was called Norwalk virus, and later the name was given to all noroviruses. The Norwalk virus is a genogroup I NoV (GI.1). GI NoVs are common in foodborne and waterborne outbreaks of GE, which may occur in any age group. Conceivably such outbreaks are more difficult to target by vaccination, although some special groups such as cruise ship passengers and military recruits could be targeted.

In contrast, the epidemic NoV GE in children has a predictable seasonal pattern and occurs every winter. The age distribution is similar to that of RV GE (Fig. 25.1), and a vaccination approach should be targeted at infants or toddlers at the latest. In epidemic NoV GE, the predominant viruses are of genogroup II, particularly genotype GII.4, which is also the prime candidate for NoV vaccine development. There are at least 22 genotypes of NoVs within genogroup II and 9 genotypes within genogroup I. Repeated NoV infections and episodes of GE occur in young children. The resulting immunity is serotype-specific and not long lasting. A NoV vaccine could not possibly contain all genotypes, and a changing composition (such as influenza vaccine) would also be difficult. Therefore, it is commonly held that a NoV vaccine should contain both genogroups, but induce cross-protective immunity within the genogroup.

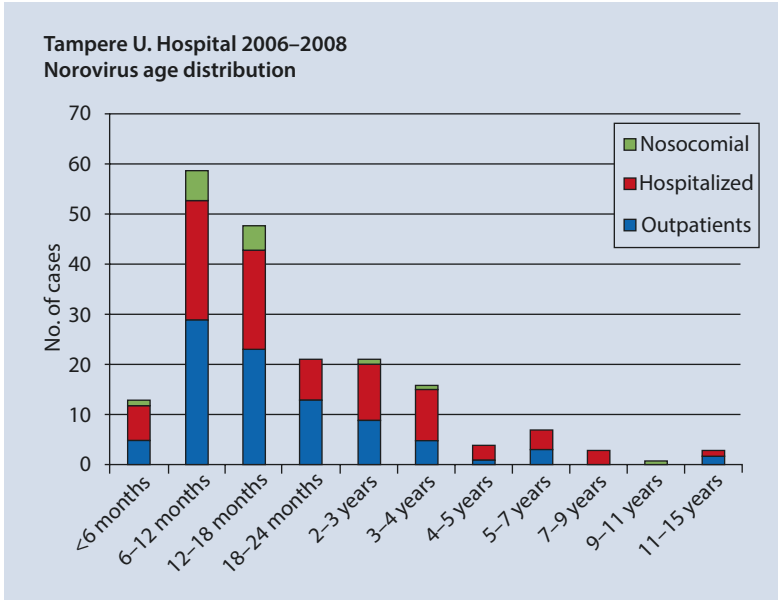


Fig. 25.1 Age distribution of NoV gastroenteritis in Tampere University Hospital 2006–2008. (Reproduced with permission. Räsänen S, PhD thesis. University of Tampere 2016)

25.2 Norovirus Vaccine Development

Noroviruses do not grow in normal cell culture and only poorly in explants of gut tissue. Therefore, a live virus is not regarded as an option. Most probable candidate vaccines are NoV virus-like particles (VLPs), which can be produced in baculovirus insect cell system or in plants. VLPs are highly antigenic and may be administered either by injection or mucosally (e.g., intranasally). Only one NoV VLP vaccine has progressed to phase II/III clinical trials. This vaccine is produced by Takeda (by acquiring LigoCyte). It is a bivalent NoV GI.1 + GII.4 VLP vaccine combined with aluminum adjuvant. The GII.4 component is based on a "consensus" sequence and is not any variant that occurs in nature. The idea is that such a consensus VLP induces a cross-reacting immune response and elicits protection against other GII.4 variants and, possibly, more broadly, against other GII NoVs.

The results of a proof-of-concept challenge trial in adult volunteers are shown in Table 25.1. In this study, the subjects received two doses of Takeda's candidate NoV VLP vaccine and were challenged on day 42 with a naturally occurring wild-type GII.4 NoV Farmington strain. The results indicate that the vaccine induced partial protection against heterologous challenge. Specifically, there was high-level protection against severe NoV GE, less against mild NoV GE, and no protection against NoV infection.

Table 25.1 Results of a norovirus GI/GII VLP vaccine (Takeda) challenge study

Outcome	Protection (%)	*p*
Severe vomiting/diarrhea	100	0.054
Moderate to severe vomiting/diarrhea	68	0.068
Any vomiting/diarrhea	47	0.074
Infection	14	0.420

Adapted from Bernstein et al. (2015)
A total of 50 vaccinees and 48 control subjects. A NoV vaccine containing a consensus sequence of GII.4 was given intramuscularly in two doses to healthy adult volunteers followed by challenge on day 42 with GII.4 Farmington strain NoV

The NoV challenge study experience resembles the performance of the RV vaccine in that a NoV VLP vaccine seems to prevent severe disease and not NoV infection. This should be seen as a realistic target for a future NoV vaccine in children. A parenteral vaccine given in two or three doses to infants or toddlers would induce broadly reactive cross-protection against severe NoV, but would not fully prevent NoV infection with mild symptoms. Even so, a successful NoV vaccine would do better than nature.

Takeda's bivalent NoV GI.1 + GII.4 VLP vaccine has also been tested for immunogenicity and safety in children. The studies have established that the GI.1 component is much more immunogenic than GII.4 in the combination, and a future vaccine should certain a larger quantity of GII.4, than of GI.1.

Takeda now has completed an efficacy trial in adults of their vaccine candidate TAK-214 containing 15 μg of GI.1 and 50 μg of GII.4. The study was conducted in about 4700 US Army recruits. Two doses of the vaccine gave 62% (2183) protection against moderate to severe NoV GE caused by any NoV genotype.

Another Japanese company, Denka, has produced a bivalent NoV VLP vaccine in *Nicotiniana benthamiana* tobacco plants. This vaccine is in phase I trials in adults.

A different candidate NoV vaccine has been produced using adenovirus Ad5 as a vector. The vector expresses NoV capsid proteins of NoV GI.1 and GII.4, and is administered orally. The same company, Vaxart, is using the same approach for oral coronavirus vaccine development.

A future option is the combination of NoV VLP vaccine with rotavirus VP6. In this combination, RV VP6 would not only protect against RV GE, but also enhance the immune response to NoV, like an adjuvant. Such a combination has the potential of becoming a universal vaccine against childhood GE.

Further Reading

Atmar RL, Bernstein DI, Harro CD, et al. Norovirus vaccine against experimental human Norwalk virus illness. N Engl J Med. 2011;365:2178–87.

Bernstein DI, Atmar RL, Lyon GM, et al. Norovirus vaccine against experimental human GII.4 virus illness: a challenge study in healthy adults. J Infect Dis. 2015;95:2734–47.

Blazevic V, Lappalainen S, Nurminen K, Huhti L, Vesikari T. Norovirus VLPs and rotavirus VP6 protein as combined vaccine for childhood gastroenteritis. Vaccine. 2011;29(45):8126–33.

Blazevic V, Malm M, Arinobu D, Lappalainen S, Vesikari T. Rotavirus capsid VP6 protein acts as an adjuvant in vivo for norovirus virus-like particles in a combination vaccine. Hum Vaccin Immunother. 2016;12(3):740–8.

Esposito S, Principi N. Norovirus Vaccine: priorities for future research and development. Front. Immunol 2020; fimmu.2020.01383.

JCON Genetics press release.

Kapikian AZ, Wyatt RG, Dolin R, Thornhill TS, Kalica AR, Chanock RM. Visualization by immune electron microscopy of a 27-nm particle associated with acute infectious nonbacterial gastroenteritis. J Virol. 1972;10:1075–81.

Kim L, Liebowitz D, Lin K, Kasparek K, Pasetti MF, Garg SJ et al. Safety and immunogenicity of an oral tablet norovirus vaccine, a phase I randomized placebo-controlled trial. JCI Insight 2018;3:13. e121077.

Lopman BA, Hall AJ, Currs AT, Parashar UD. Increasing rates of gastroenteritis hospital discharges in US adults and the contribution of norovirus, 1996–2007. Clin Infect Dis. 2011;52:466–72.

Masuda T, Lefevre I, Mendelman P, Sherwood J, Bizjajeva S, Borkowski A. Immunogenicity of Takeda's bivalent virus-like particle (VLP) norovirus vaccine (NoV) candidate in children from 6 months up to 4 years of age. Open Forum Infect Dis 2018;5(suppl 1):674.

Pang XL, Joensuu J, Vesikari T. Human calicivirus-associated sporadic gastroenteritis in Finnish children less than two years of age followed prospectively during a rotavirus vaccine trial. Pediatr Infect Dis J. 1999;18:420–6.

Prasad BV, Rothnagel R, Jiang X, Estes MK. Three dimensional structure of baculovirus-expressed Norwalk virus capsids. J Virol. 1994;68:5117–25.

Räsänen S, Lappalainen S, Salminen M, Huhti L, Vesikari T. Noroviruses in children seen in a hospital for acute gastroenteritis in Finland. Eur J Pediatr. 2011;170(11):1413–8.

Sherwood J, Mendelman PM, Lloyd E, Liu M, Boslego J, Borkowski A, Jackson A, Faix D, US Navy Study Team. Efficacy of intramuscular bivalent norovirus GI.1 / GII.4 virus like particle vaccine candidate in healthy US adults. Vaccine 2020;38(41):6442−9.

Vesikari T, Blazevic V. Norovirus vaccine: one step closer. J Infect Dis. 2015;211:853–5.

RSV Vaccines and Monoclonal Antibodies in Development

Eva P. Galiza, Paul T. Heath, and Simon B. Drysdale

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_26

26.1 Respiratory Syncytial Virus (RSV)

RSV is a medium-sized RNA virus and is classified as a paramyxovirus. Its genome encodes for 10 proteins; two of these are non-structural proteins and eight are structural proteins. There are three transmembrane surface glycoproteins, of which two, a fusion protein (F) and an attachment protein (G), are responsible for the initiation and propagation of infection. There are two subtypes of RSV: Types A and B. They differ primarily in the composition of the G protein, while the F protein is conserved between the two strains.

26.2 RSV Disease

Infection with RSV causes disease ranging from mild upper respiratory tract infection (URTI) to severe lower respiratory tract infection (LRTI) (e.g. bronchiolitis in young infants) which can result in the need for intensive care and even death. There may be up to 120,000 deaths each year due to RSV infection in children under 5 years globally, approximately 99% of which occur in low- and middle-income countries (LMIC). In 2015, there were an estimated 33.1 million cases of RSV-associated acute LRTI in infants under 5 years of age every year (22% of ALRI episodes), 3.2 million resulting in hospital admission, and RSV is estimated to account for 3–9% of all fatal LRTIs in infants.

RSV infection is seasonal in most countries; outbreaks occur most frequently in the cold season in areas with temperate and Mediterranean climates and in the wet season in tropical countries with seasonal rainfall. Young age is the major risk factor for RSV disease, with hospital admissions peaking at about 8–12 weeks of age and disease generally becoming less severe after 6 months of age. A number of genetic and environmental factors combine with the age of the infant to increase the risk of severe RSV disease. Infants with certain co-morbidities including prematurity, bronchopulmonary dysplasia, congenital heart disease, immunodeficiency, cerebral palsy, and Down's syndrome are known to be at high risk from more severe RSV infections. Nevertheless, the majority of acute hospital admissions occur in otherwise healthy infants born at term.

26.3 Monoclonal Antibodies

The humanized mouse monoclonal antibody (mAb) palivizumab, which binds to an antigenic site (site II) of the RSV fusion (F) protein, has been available for prophylaxis against RSV infection for high-risk infants since 1998. It is up to 80% effective in preventing hospitalization due to RSV infection in some subgroups of high-risk infants. It is expensive and due to a relatively short half-life (approximately 20 days) requires 5 monthly intramuscular injections over the RSV season. Its use is therefore restricted to only the highest risk groups.

Since then, other mAbs have been in development. Motavizumab, a similar product, has an in vitro affinity for the RSV F protein 100 times that of palivizumab. However, clinical trials did not show any increased efficacy compared with palivizumab and its development was stopped. Suptavumab was another RSV mAb that showed promise in Phase 2 trials but unfortunately in a phase 3 trial failed to achieve its primary end point of a reduction in medically attended RSV infection and its development was stopped. It was subsequently shown that Suptavumab offered little protection against infection with RSV-B.

Another anti-RSV mAb, RB1, is a fully human mAb (IgG1) with a binding epitope in the highly conserved antigenic site IV of the RSV F protein. The binding epitope of RB1 is conserved with 99.9% identity, and antigenic site IV is more conserved overall compared with sites Ø, II, and V. MK-1654 is derived from RB1 and is being tested in clinical trials. In a phase 1 study, it was shown to be safe and tolerable and had a serum half-life of 73 to 88 days, potentially allowing a single dose to protect infants for a whole RSV season.

Treatment-emergent antidrug antibodies were low (2.6%). Phase 2 and 3 clinical trials in term and preterm infants are currently underway.

Nirsevimab (MEDI8897) is a novel monoclonal antibody targeted at prefusion conformation of F protein, that has recently entered Phase 3 trials in term and preterm infants. Results from a Phase 2 trial show it is safe to use in otherwise healthy preterm infants and it reduced medically attended RSV LRTI by 70% and hospitalization for RSV-associated LRTI by 78% compared with placebo at 150 days after dosing. Nirsevimab has the advantage of once a season dosing due to a long half-life (approximately 83–94 days). Because of the great medical need and promising Phase 2 trial results, nirsevimab has been granted a fast-track status by FDA and EMA for evaluation for licensure. It is expected that the price of nirsevimab will be considerably less than that of palivizumab.

26.4 Vaccines

Vaccine development for RSV started soon after RSV was identified in 1956 but stalled for several decades as a result of a trial in the 1960s with a formalin-inactivated RSV vaccine. This resulted in enhanced, including fatal, cases of RSV disease in vaccine recipients. However, the field is now flourishing; 36 candidates are currently (as of March 2020) under development, including 17 undergoing clinical trials.

Vaccine strategies being considered for protecting infants include infant vaccination, maternal vaccination, and vaccinating contacts of infants in order to prevent transmission. Maternal immunization, which aims to provide protection to the infant by boosting the levels of transplacental antibody, is the leading strategy.

The most advanced candidates are subunit vaccines containing purified RSV F protein. Only one Phase 3 study in pregnant women has completed. It included 4636 pregnant women and was demonstrated to be immunogenic, safe, and well tolerated by both the women and their infants. It demonstrated a vaccine efficacy (VE) of 39.4% (97.5% CI: −1.0 to 63.7%) in reducing medically significant RSV infection by 90 days of life in infants of mothers who received the vaccine which unfortunately meant it narrowly failed to meet its primary endpoint. It did, however, meet its secondary endpoint of preventing RSV hospitalization (VE 44.4% [95% CI: 19.6 to 61.5%]). Interestingly, the vaccine also showed some protection against all cause medically significant LRTIs and against hospitalization and severe hypoxaemia due to all cause LRTIs (VE 23.2%, 27.7%, and 46.0%, respectively), with a suggestion that vaccination earlier in pregnancy was more effective. This study gives great promise that a safe and efficacious maternal RSV vaccine can be developed, indeed other F protein-based efficacy trials are being planned.

Vaccines designed for infants need to overcome the difficulties of generating a protective response at this age and the theoretical risks associated with generating an inappropriate response. Current candidates include gene-based vector vaccines (e.g. adenovirus), particle-based, subunit, and live-attenuated vaccines. Only three vaccines are currently being tested in Phase 2 clinical trials (none are in Phase 3). Two vaccines use a viral vector to express the RSV F protein (in the pre-fusion conformation) and are being tested in seropositive infants 12–24 months old. One vaccine uses a chimpanzee-derived adenovector (ChAd155-RSV) and the other an adenovirus serotype 26 vector. The third vaccine is a live-attenuated RSV vaccine which is being tested in seronegative infants 6–18 months old.

For infants in LMICs, where children up to 5 years of age continue to suffer severe RSV disease, boosting maternal antibody alone may not be a sufficient strategy to protect infants for the entire risk period. Paediatric vaccines will therefore become a necessary part of a complete prevention strategy. Such vaccines could be administered at a later time point in infancy when the effect of maternal vaccination or neonatally administered monoclonal antibody wanes.

Further Reading

Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med. 2009;360(6):588–98.

Kapikian AZ, Mitchell RH, Chanock RM, Shvedoff RA, Stewart CE. An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. Am J Epidemiol. 1969;89(4):405–21.

Munoz FM. Respiratory syncytial virus in infants: is maternal vaccination a realistic strategy? Curr Opin Infect Dis. 2015;28(3):221–4.

Murray J, Bottle A, Sharland M, Modi N, Aylin P, Majeed A, et al. Risk factors for hospital admission with RSV bronchiolitis in England: a population-based birth cohort study. PLoS One. 2014;9(2):e89186.

Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. Pediatrics. 1998;102(3 Pt 1):531–7.

PATH. Respiratory syncytial virus vaccine and mAb snapshot 2020 [25/01/21]. Available from: https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/

Openshaw PJM, Chiu C, Culley FJ, Johansson C. Protective and Harmful Immunity to RSV Infection. Annu Rev. Immunol. 2017 Apr 26;35:501–532. doi: https://doi.org/10.1146/annurev-immunol-051116-052206. Epub 2017 Feb 6.

Antonios O, Aliprantis, Dennis Wolford, Luzelena Caro, Brian M Maas, Hua Ma, Diana L Montgomery, Laura M Sterling, Allen Hunt, Kara S Cox, Kalpit A Vora, Brad A Roadcap, Radha A Railkar, Andrew W Lee, S Aubrey Stoch, Eseng Lai. A Phase 1 Randomized, Double-Blind, Placebo-Controlled Trial to Assess the Safety, Tolerability, and Pharmacokinetics of a Respiratory Syncytial Virus Neutralizing Monoclonal Antibody MK-1654 in Healthy Adults. Clin Pharmacol Drug Dev. 2020 Oct 30. doi: https://doi.org/10.1002/cpdd.883. Online ahead of print.

Madhi SA, Polack FP, Piedra PA, Munoz FM, Trenholme AA, Simões EAF, Swamy GK, Agrawal S, Ahmed K, August A, Baqui AH, Calvert A, Chen J, Cho I, Cotton MF, Cutland CL, Englund JA, Fix A, Gonik B, Hammitt L, Heath PT, de Jesus JN, Jones CE, Khalil A, Kimberlin DW, Libster R, Llapur CJ, Lucero M, Pérez Marc G, Marshall HS, Masenya MS, Martinón-Torres F, Meece JK, Nolan TM, Osman A, Perrett KP, Plested JS, Richmond PC, Snape MD, Shakib JH, Shinde V, Stoney T, Thomas DN, Tita AT, Varner MW, Vatish M, Vrbicky K, Wen J, Zaman K, Zar HJ, Glenn GM, Fries LF; Prepare Study Group. Respiratory Syncytial Virus Vaccination during Pregnancy and Effects in Infants. N Engl J Med. 2020 Jul 30;383(5):426−439. doi: https://doi.org/10.1056/NEJMoa1908380.

Griffin MP, Yuan Y, Takas T, Domachowske JB, Madhi SA, Manzoni P, Simões EAF, Esser MT, Khan AA, Dubovsky F, Villafana T, DeVincenzo JP; Nirsevimab Study Group. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. N Engl J Med. 2020 Jul 30;383(5):415–425. doi: https://doi.org/10.1056/NEJMoa1913556.

Li Y, Reeves RM, Wang X, Bassat Q, Brooks WA, Cohen C, Moore DP, Nunes M, Rath B, Campbell H, Nair H; RSV Global Epidemiology Network; RESCEU investigators. Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis. Lancet Glob Health. 2019 Aug;7(8):e1031−e1045. doi: https://doi.org/10.1016/S2214-109X(19)30264-5.

Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, Polack FP, Balsells E, et al; RSV Global Epidemiology Network. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet. 2017 Sep 2;390(10098):946–958. doi: https://doi.org/10.1016/S0140-6736(17)30938-8. Epub 2017 Jul 7.

COVID-19 in Children and COVID-19 Vaccines

Elizabeth Whittaker and Paul T. Heath

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_27

27.1 SARS-CoV-2

Coronaviruses comprise a large family of enveloped single-stranded, zoonotic RNA viruses. Human coronaviruses (HCoV) infections range from the common cold to severe diseases including bronchitis, pneumonia, severe acute respiratory distress syndrome (ARDS), multi-organ failure and death. Coronaviruses commonly circulate in animals (including bats, livestock, and birds). They are able to rapidly mutate leading to novel coronaviruses, that can spread from animals to humans. This occurred in China in 2002 when the novel coronavirus severe acute respiratory syndrome coronavirus (SARS-CoV) emerged, in Saudi Arabia in 2012 when the Middle East Respiratory Syndrome coronavirus (MERS-CoV) was transmitted from dromedaries to humans, and most recently when severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was announced following a cluster of adults with pneumonia in Wuhan, Hubei Province, China on 31 December 2019. The term COVID-19 is used to describe the clinical disease caused by SARS-CoV-2.

27.2 Epidemiology

Human-to-human transmission from symptomatic and asymptomatic persons is the main driver of spread, with a median incubation period of 5–6 days.

The main basis for diagnosis of SARS-CoV-2 is real-time polymerase chain reaction (RT-PCR) on upper or lower respiratory secretions, usually nasopharyngeal swab. Rapid tests–based antigen detection have also been developed. Antibody tests can be used to detect past infection.

Subsequently, seroprevalence studies have shown lower seroprevalence in children than adults. Studies have confirmed that younger children in particular are less likely to have antibody to SARS-CoV-2, with one Swiss population-based study showing a seroprevalence of 0.8% in children 5–9 years and 9.6% in children 10–19 years, compared to a population seroprevalence of 10.8%. Initial case series suggested that most cases in children resulted from household exposure; however, these findings must be interpreted with caution because of pandemic mitigations limiting the exposure of children to close contacts outside of their households. Although some studies have shown transmission within family groups and in schools, there remains limited evidence to quantify the extent to which children contribute to overall transmission.

27.3 Burden of Disease

The majority of children with SARS-CoV-2 infections are asymptomatic or have mild disease. Worldwide, severe disease and deaths are mostly observed in children with associated co-morbidities; these included being 'medically complex' (40%), immunosuppressed (23%), obese (15%), and diabetic (8%) in one North American Study. In US and European surveillance studies, age under 1 year of age and underlying medical conditions were associated with critical care admission. Interestingly, children with underlying cancer diagnoses, or those who are immunosuppressed, do not appear to have increased susceptibility to infection, however, as they are likely to have been actively 'shielding' from exposure during the pandemic, further data on the rate and severity of COVID-19 in these groups is needed.

A review of childhood mortality from COVID-19 from seven countries across three continents from March to May 2020 reported that deaths in children with COVID-19 accounted for only 0.3% of all COVID-19 deaths.

In April 2020, reports of an inflammatory condition with overlapping features of Kawasaki disease and Toxic Shock Syndrome emerged in Italy and the UK, and subsequently countries in Europe, the Americas, and Asia have reported cases of this rare syndrome, now called Paediatric Inflammatory Multisystem Syndrome (PIMS-TS) or Multisystem Inflammatory Syndrome in Children (MIS-C), that is temporally associated with SARS-CoV-2 infection. Case definitions use criteria

including clinical manifestations (fever, inflammation, organ dysfunction), elevated biochemical markers of inflammation, and evidence of contact or infection with SARS-CoV-2, with exclusion of another microbial cause. In the largest reported cohort, the median age of disease is around 8 years (range 2 weeks–20 years); 55% are male, and 1.8% died. Although co-morbidities are generally uncommon in this patient cohort, obesity has been identified as a risk factor in the USA. SARS-CoV-2 PCR positivity is uncommon (median 18%), but seropositivity is more common (range 50–95%). Cardiovascular complications were frequent (40%) in UK and USA cohorts, with 14–18% of cases developing coronary artery aneurysms. Long-term outcome data for this cohort is urgently required.

27.4 Vaccines

Given the burden of COVID-19, it was clear at an early stage that the rapid development, distribution, and administration of a vaccine to the global population would be the most effective approach to suppress the pandemic. However, it was also apparent that there were huge challenges in vaccine design, manufacture at scale, and global distribution to overcome.

Development of candidate COVID-19 vaccines was made possible by the early availability of genomic and structural information of the virus itself. There was also considerable knowledge gained from the prior development of SARS/MERS vaccine candidates, although none were licensed and no immunological correlates of protection were established. The adoption of a continuous Phase I/II/III trial strategy has also been an important factor, a model that can now be applied to reduce the protracted development timelines that have often delayed the availability of vaccines against other important infectious diseases.

The first vaccine to be given to humans was the Moderna RNA vaccine (mRNA-1273), which entered its Phase I trial on March 16, 2020, an astonishing 63 days after sequence selection. This candidate represents a new vaccine platform technology and, although more traditional platforms are being employed, the use of new technologies, for which there are no previously licensed examples, is a particular feature of the COVID-19 vaccine field. As of February 1, 2021, there are an estimated 292 vaccine candidates, of which 70 are in clinical trials (▶ https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/, accessed 1/2/21). A common feature of nearly all vaccine candidates, however, is that they use the Spike (S) protein of the SARS-CoV-2 virus as an immunogen, in recognition of its significance in ACE2 receptor binding and subsequent disease pathogenesis. The largest single group of vaccine types are the protein subunit vaccines consisting of S-protein or nanoparticles thereof. Several mRNA vaccines have either been licensed or are soon forthcoming, whereas no DNA vaccine appear to be near. Adenovirus vectored vaccines have also made a breakthrough. More conservative approach is inactivated whole virus. Such vaccines are made in China, with worldwide distribution, and also in India and Russia.

Table 27.1 summarises data on COVID-19 vaccines with reported efficacy data as of 1/2/21.

Table 27.1 Groups of COVID-19 vaccines and the key representatives of each group with reported efficacy data

mRNA vaccines	BioNTech/Pfizer	95%
	Moderna	94%
	(Curevac)	70%
Ad-vector vaccines	Oxford/AstraZeneca	66%[a]
	Janssen (J&J)	66%
	Gamaleya	92%
Protein Vaccines	Novavax	89%
Inactivated whole virus vaccines	Sinovac	50–91%[b]
	SinoPharm	79%

[a]1 dose only
[b]Various country trials reported

27.4.1 RNA Vaccines

The potential advantages of this technology, in which the RNA sequence of the antigen of interest is identified and then enclosed within a delivery system, is that it results in natural antigen expression. In principle, its simplicity means that large-scale production of vaccine can be faster and more standardised than that of traditional vaccines. It also does not require special delivery devices (as with DNA vaccines) and there is no risk of its integration with host DNA.

Nevertheless, although human Phase I and II clinical trials have been conducted with RNA vaccines against a range of important infections, none had progressed to efficacy trials and none had been licensed – before the COVID-19 vaccines.

Although the Moderna RNA vaccine was first into clinical trials, it was in fact the BioNTech/Pfizer RNA vaccine that first reported efficacy against COVID-19. This vaccine (BNT162b2) encodes the SARS-CoV-2 full-length spike, modified by 2 proline mutations (P2 S) to lock it in the prefusion conformation. The chosen dose was 30 ug and a two-dose schedule (0/21 days) was assessed in a 43,548 participant Phase III trial, predominantly (77%) recruiting in the USA. Among participants who had no evidence of existing or prior SARS-CoV-2 infection, 8 cases of symptomatic COVID-19 were observed >7 days after the second vaccine dose as compared with 162 cases in the saline placebo group, an efficacy of 95% (95% CI 90.3 to 97.6). Only 10 severe cases were reported after the first dose of study vaccine of which 9 were in the placebo group. It was also shown that a similar range of efficacies (90–100%) existed across a number of important subgroups (older age, sex, race and ethnicity, BMI, coexisting conditions). Reactogenicity was defined in a subgroup and was common (e.g. fatigue 62.9%, headache 55.1%, chills 31.9%, fever 14.2%) although there were no significant differences in SAEs between groups. Reactogenicity was more pronounced after the second dose and was less frequent overall in the elderly cohort. Of interest there were 4 cases of Bell's palsy (vs 0 placebo) and 64 of lymphadenopathy (vs 6) in the vaccinated group. The first regulatory approval for this vaccine was given by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) on 2 December 2020 followed by the United States Food and Drug Administration (US FDA) on 11 December 2020.

The Moderna (mRNA) vaccine was the second COVID-19 vaccine to report efficacy. This is a lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine that encodes for a full-length, prefusion spike (S) protein and stabilised in its prefusion conformation by two consecutive proline substitutions at amino acid positions 986 and 987, at the top of the central helix in the S2 subunit. The LNP capsule is composed of four lipids and the vaccine is formulated in a fixed ratio of mRNA and lipid. The Phase III trial recruited 30,420 volunteers, all in the USA. At the time of this analysis the median follow-up of participants was 64 days. Symptomatic Covid-19 occurring >14 days after the second dose was reported in 185 placebo and 11 vaccine recipients: an efficacy of 94.1% (95% CI, 89.3 to 96.8%). Severe Covid-19 was reported in 30 participants (including 1 death), all in the placebo group. Again, there were no significant safety concerns and reactogenicity was higher after the second dose and less frequent in the elderly cohort. This vaccine received regulatory approval from the FDA on 18 December 2020.

The third mRNA vaccine expected for licensure is made by Curevac. The manufacturer has packed mRNA in 'microfactories', which they claim can be distributed for production globally.

27.4.2 Adenovirus-Vectored Vaccines

Adenoviruses appear to be potent vectors for inducing and boosting cellular immunity to encode recombinant antigens because the immunogen is being expressed in the context of a heterologous viral infection. However, vaccines based on some human adenoviruses

may have limited potential due to pre-existing population immunity. An alternative therefore is the use of a non-human adenovirus and this is one of the reasons for the use of a replication-deficient Chimpanzee adenovirus by the University of Oxford/AstraZeneca candidate. The ChAdOx platform was previously used to develop vaccines against a range of other pathogens, although none have been licensed.

The ChAdOx COVID-19 vaccine was reported to be effective following an interim analysis of four RCTs in Brazil, South Africa and the UK. These trials include 23,848 participants of which 11,636 (7548 in the UK) contributed to this interim primary analysis. At the time of this analysis, there were 131 COVID-19 cases reported more than 14 days after a second dose, 30 in the vaccine group and 101 in the control or placebo groups: an efficacy of 70.4% (54.8–80.6%). From 21 days after the first dose, there were 10 cases hospitalised for COVID-19, all in the control arm; two were classified as severe COVID-19, including one death. There were no safety reports of concern. Preliminary analyses suggest better efficacy with longer intervals between doses (up to 12 weeks).

The second Ad-vector vaccine is made by Janssen (Johnson & Johnson) and is expected to be licensed in EU soon. The vaccine uses Ad26 as a vector. The manufacturer has previous experience of the same Ad-vector in the production of an Ebola vaccine.

Russian made Ad-vector COVID-19 vaccine is produced by Gamaleya Institute in Moscow. Also this laboratory had previous experience of Ad-vectors for the development of Ebola vaccine. The Russian vaccine, called Sputnik V, uses Ad26 vector for the first dose and Ad5 for the second dose, avoiding potential inhibiting effect on the uptake of second dose. A study in Russia and Belarus reported a 92% efficacy.

27.4.3 COVID-19 Vaccines in Children

As summarised earlier, less than 5% of COVID-19 cases are in children and in general they have mild disease. The exception to this is the severe inflammatory syndrome (PIMS-TS/MIS-C); however, this is extremely rare. A further rationale for justifying inclusion of children in a COVID-19 vaccination programme then (as with influenza), would be their role in population transmission. Nevertheless, it remains likely that if there is ongoing circulation of SARS-CoV-2 in children, it will ultimately be transmitted to any adults who remain susceptible.

For these reasons, a number of vaccine manufacturers have proposed or initiated studies in children and adolescents with the purpose of ultimately extending COVID-19 vaccination to adolescents and children, possibly in this order.

At this time vaccines are not recommended for children under 16 years of age. In the UK, however, national guidance has proposed that children with severe neuro-disabilities, given their very high risk of exposure, may be considered for vaccination. In support of this, the Pfizer BioNTech COVID-19 vaccine studies did include a small number of children aged 12 years and older. It is likely that other at-risk groups will become eligible as further data from adult trials become available.

27.4.4 COVID-19: Outstanding Questions

The pace at which vaccines have been developed, tested, and implemented against this new pathogen has been truly astonishing. Many lessons have been learned along the way, but more questions remain. These are summarised in this section.

How long will vaccine protection last? The length of follow-up in the published trials is relatively short (a median of 2–3 months), and thus it is not yet possible to define the duration of protection afforded by current vaccines. All of the trials continue, and this will become clear, including whether or not booster doses of vaccine will be required.

Are these vaccines really safe? The published Phase 3 trials involve many thousands of participants (11–43,000) and there have

been no significant safety concerns identified. However, very rare but important adverse events may not be detected even in trials of this size and may only become apparent after many hundreds of thousands of people have been vaccinated. For example, following the implementation of the Pfizer and Moderna vaccines in the UK and USA, there have been multiple reports of anaphylaxis, in excess of what might be expected following routine vaccines. Enhanced surveillance for safety issues is a prerequisite for all vaccine programmes.

What level of immunity is needed for protection? It is generally accepted that high levels of neutralising antibody against the S-protein of SARS-CoV-2 is critical to protection, although cell-mediated immune responses may well be important also. The ability to define the precise levels of a protective immune response (i.e. the serocorrelate of protection (CoP)) will provide enormous advantages such as the ability to bridge results between different vaccines or populations. All current studies have the definition of a CoP as an objective.

Do vaccines protect against disease or infection or both? This question is particularly important when considering the potential impact of vaccines on transmission (above and beyond their ability to directly protect the vaccinee against symptomatic disease). It is not yet clear from published studies whether these vaccines can prevent infection, and further insight will be gained through enhanced surveillance post implementation. However, current trials are investigating whether there is protection against asymptomatic infection (in addition to symptomatic infection) and results are awaited.

Do vaccines work for all people, including in those at high risk of COVID-19? By definition, although all trials have included a range of participants based on age, ethnicity and comorbidities, many of those in the populations at very high risk of COVID-19 may have been excluded from participation. Conclusions about the efficacy in such groups are therefore limited. It is likely that for such groups specific studies will need to be done to address whether they are able to produce equivalent immune responses and whether they are safe. A particular example of this is pregnant and breastfeeding women. Several of the vaccine companies are actively planning specific studies for this special group.

What are the implications of new variants? At this time there are rapidly spreading variants of SARS-CoV-2, especially in the UK, South Africa and Brazil. These variants have multiple mutations in the S protein and there is therefore concern that they may render the virus less susceptible to current vaccines. A range of in vitro studies are in progress to address this. Preliminary efficacy data from the UK, however, suggests that the Novavax vaccine remains effective, at least against the UK and South African variants, albeit with lower efficacy against the South African strain (◘ Table 27.1). A similar (preliminary) conclusion is drawn for the Janssen vaccine against the South African strain. Recently, an Indian variant, also called delta, has caused a surge of COVID_19 not only in India but also the UK and several European countries. It is evident that one dose of the current vaccine is not sufficient to limit the spread of delta variant but two doses will be required for clinical protection and for control of transmission. There also is the real prospect of rapidly modifying vaccines to account for these strains, a tribute to the technologies and landscape that have evolved to deal with the COVID-19 pandemic.

Further Reading

Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2020 Dec 30:NEJMoa2035389. doi: https://doi.org/10.1056/NEJMoa2035389.

Boulad F., Kamboj M., Bouvier N., Mauguen A., Kung A.L. COVID-19 in children with cancer in New York City. JAMA Oncol. 2020

Dong, Y. et al. (2020) 'Epidemiology of COVID-19 Among Children in China', *Pediatrics*. American Academy of Pediatrics, 145(6). doi: https://doi.org/10.1542/PEDS.2020-0702

Godfred-Cato S, Bryant B, Leung J, et al. COVID-19-Associated Multisystem Inflammatory Syndrome in Children - United States, March-July 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**(32): 1074–80.

Götzinger, F. et al. (2020) 'COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study', *The Lancet. Child & Adolescent*

Health. Elsevier, 4(9), p. 653. doi: https://doi.org/10.1016/S2352-4642(20)30177-2.

Li X, Xu W, Dozier M, He Y, Kirolos A, Lang Z, Song P, Theodoratou E; UNCOVER. The role of children in the transmission of SARS-CoV2: updated rapid review. J Glob Health. 2020 Dec;10(2):021101. doi: https://doi.org/10.7189/jogh.10.021101. PMID: 33312511; PMCID: PMC7719356.

Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020 Dec 31;383(27):2603–2615. doi: https://doi.org/10.1056/NEJMoa2034577.

The Royal College of Paediatrics and Child Health **Guidance–paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS).** https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims Date: 2020

Shekerdemian L.S., Mahmood N.R., Wolfe K.K. Characteristics and outcomes of children with Coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. JAMA Pediatr. 2020

Stringhini, S. et al. (2020) 'Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study', *The Lancet*. Elsevier, 396(10247), pp. 313–319. doi: https://doi.org/10.1016/S0140-6736(20)31304-0.

Viner RM, Ward JL, Hudson LD, et al. Systematic review of reviews of symptoms and signs of COVID-19 in children and adolescents *Archives of Disease in Childhood* Published Online First: 17 December 2020. doi: https://doi.org/10.1136/archdischild-2020-320972

Viner, R. M. et al. (2020) 'Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared with Adults', *JAMA Pediatrics*. doi: https://doi.org/10.1001/jamapediatrics.2020.4573.

Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021 Jan 9;397(10269):99–111. doi: https://doi.org/10.1016/S0140-6736(20)32661-1.

Whittaker, E. et al. (2020) 'Clinical Characteristics of 58 Children with a Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2', *JAMA*. American Medical Association, 324(3), p. 259. doi: https://doi.org/10.1001/jama.2020.10369.

Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727–733.

Registration of Vaccines, Safety Follow-Up, and Paediatric Investigation Plan

Carlo Giaquinto and Francesca Rocchi

Contents

T. Vesikari, P. Van Damme (eds.), *Pediatric Vaccines and Vaccinations*,
https://doi.org/10.1007/978-3-030-77173-7_28

28.1 Standard Vaccine Development

Vaccine development is difficult, complex, highly risky, and costly, and includes clinical development, process development, and assay development. The risk is high because most vaccine candidates fail in preclinical or early clinical development due to a variety of reasons such as not fully understanding the biology of protection, lack of good animal models to predict vaccine behaviour in humans, unpredictability of human immune system reactions to antigens as it relates to immunogenicity or safety, the unpredictability of the impact of combining multiple components in a vaccine.

Vaccines process development is generally a lengthy process and registrative studies are mostly done in sequential steps. It involves making preparations of the test vaccine that satisfy regulatory requirements for clinical testing including clinical lots, preclinical toxicology testing, and analytical assessment, and finally scale-up methods that lead to a consistent manufacturing process. Usually three consecutive lots are tested in the clinic for immunogenicity. Assay development involves the definition of specific methods to test the purity of raw materials, stability, and potency of the vaccine product, and immunologic and other criteria to predict vaccine efficacy. Go/no-go decisions must be made at each stage of clinical and process development and must be data driven. Clinical, process, and assay development tasks must be closely integrated.

Vaccines developers first make small batches and do small-scale studies to characterize and optimize the production process. They perform studies to determinate a suitable formulation that can keep vaccine components stable to the end of its shelf life. Then the developer decides whether to continue development and scale up production. To assure that the vaccine meets its intended quality profile and complies with regulatory standards, the company develops a suitable and effective quality control strategy. Studies on pharmaceutical quality look at the individual vaccine components, the final formulation to be used, and at the whole manufacturing process in detail. The vaccine developer conducts more studies in laboratory models, using in vitro studies or animal models (in vivo studies), to show how the vaccine triggers an immune response and works to prevent infection. This is followed by a clinical testing programme in humans.

Clinical development involves studies to be conducted in a large number of people in order to test the effects of vaccines on patients for safety, immunogenicity, and efficacy through a staged process that has to follow strict standards and the procedures and protocols set by the regulators. Human pharmacology studies (phase I trials) generally involve between 20 and 100 healthy volunteers to confirm if the vaccine behaves as expected based on laboratory tests. The aim is to establish if the vaccine triggers the expected immune response, if it is safe to move into larger studies, and which doses can be adequate. Therapeutic exploratory studies (phase II trials) involve several hundred volunteers. The purpose of this phase is to study the best doses to use, the most common side effects, and how many doses are needed. These studies also check whether the vaccine triggers a good immune response in a broader population. In certain cases, it could also provide some preliminary indication about vaccine efficacy. Clinical efficacy and safety studies (phase III trials) include thousands of volunteers. Phase III trials provide more definitive evidence of a vaccine's efficacy. They are usually large, randomized, blinded, and controlled studies. At the end of the testing programme, the vaccine developer submits the results to the medicines regulatory authorities in Europe as part of a "marketing authorization" application. The regulators can only approve the vaccine if its scientific evaluation of the tests results shows that the vaccine's benefits are greater than its risks.

28.2 Scientific Evaluation and Approval

In the European Union (EU), there are two types of medicines agencies marketing authorization (MA) for vaccines: the national and

the European. The national MA is issued by the National Competent Authorities (NCAs) of the individual Member States. In this case, the vaccine may be put on the market in all Member States that have granted an authorization for it. If a company is seeking a national MA in more than one Member State, the *mutual recognition* or *decentralized procedure* is available to facilitate the granting of harmonized national authorizations across Member States. For the authorization of traditional non-recombinant vaccines in the EU, the developer can submit the Marketing Authorization Application (MAA) for review to one or more national competent authorities for medicines.

On the other side, the community marketing authorization is a single authorization that allows the medicinal product to be put on the market in all Member States and is granted by the European Commission, following a positive opinion from the EMA. The EMA is a decentralized agency responsible for the scientific evaluation, supervision, and safety monitoring of medicines developed by pharmaceutical companies for use in Europe. The EMA is primarily involved in the centralized procedure for obtaining an EU MA. The Agency also gives scientific advice to companies on the development of new vaccines and develops guidelines on quality, safety, and efficacy testing requirements. Innovative vaccines and, in particular, recombinant vaccines (recombinant protein-based vaccines and recombinant viral-vectored vaccines) must be evaluated and approved in the EU via the centralized procedure. Other novel vaccines can also be approved centrally if justified by the applicant (eligibility to the centralized procedure under the 'optional scope', as outlined in Article 3 of Regulation (EC) No. 726/2004). The centralized procedure is mandatory for certain types of medicinal products and optional for others. Medicinal products made of recombinant proteins, advanced therapy medicinal products (ATMPs) for human use, human medicinal products containing a new active substance for the treatment of acquired immunodeficiency syndrome, cancer, neurodegenerative disorders, diabetes, viral diseases, auto-immune diseases/other immune dysfunctions, and designated orphan medicinal products fall within the mandatory scope and must be filed centrally at the EMA. Although the European pharmaceutical legislation does not provide a formal definition, vaccines are typically considered medicinal products containing one or more immunogenic antigens intended for the prevention of disease from infective agents. Medicinal products containing one or more immunogenic antigens for the treatment of disease, for example, chronic HIV infection, chronic hepatitis B or C infection, cancer, or Alzheimer's disease, are typically referred to as therapeutic vaccines or active immunotherapy. The same scientific principles for their product development as for prophylactic vaccines against infectious diseases apply. Vaccines against infectious diseases that are based on viral (or other) vectors or on DNA plasmids are specifically excluded from the definition of a gene therapy medicinal product (GTMP).

The scientific evaluation of the application is carried out by the Committee for Medicinal Products for Human Use (CHMP) of the EMA and a scientific opinion is prepared in co-operation with other EMA committees, as applicable, together with many expert groups and working groups, for example, the Vaccine Working Party, that contribute to the review of applications. The opinion is sent to the European Commission, which drafts a decision and, having consulted the Member States through the relevant standing committee, adopts the decision and grants a MA. In Europe, the vaccines authorized via a centralized procedure have one invented name (trade name), one common labelling, translated into 23 languages and comprises Summary of medicinal Product Characteristics (SmPC) and the user package leaflet and package labelling. Approved conditions of use are laid down in the summary of product characteristics, the SmPC (prescribing information for health professionals), the labelling, and the package leaflet for users.

Once the evaluation is completed within 210 days, the CHMP adopts a favourable or unfavourable opinion on whether to grant the authorization. Once the Community MA is granted, the EMA publishes the

CHMP assessment report on the vaccine, which includes the reasons for its opinion. This document is called the European Public Assessment Report (EPAR). The EPAR includes a summary, in all EU languages, written in a manner that is understandable to the public. EPARs and their summaries are published on the EMA website.

28.3 Safety Follow-Up

The scientific evaluation needs to show that a vaccine's benefits in protecting people against diseases are far greater than any potential risk. At the time of approval, the main body of evidence for vaccine safety and efficacy comes from large controlled, randomized clinical trials. Selected volunteers are randomly allocated to receive the vaccine being tested and followed up under controlled conditions in line with strict protocols. After approval, many people will receive the vaccine. Certain rare or very rare side effects may only emerge when millions of people are vaccinated. EU law requires that the safety of vaccines is monitored while they are in use in routine clinical practice.

The EU has a comprehensive safety monitoring and risk management (pharmacovigilance) system, which ensures measures are in place for providing advice to minimise risk, reporting suspected side effects, conducting studies after authorization, detecting any potential side effects, conducting rigorous scientific assessments of all safety data, introducing any necessary mitigating actions early on.

Competent authorities carry out safety and efficacy studies after authorization and can also require a marketing authorization holder to carry out such studies as an obligation of the authorization. Public health authorities responsible for vaccination programmes will also conduct other studies. Studies collecting effectiveness data give additional information, for example, on long-term protection or on the need for and timing of booster doses, to complement the 'efficacy' data obtained in clinical trials before the vaccine was authorized.

EMA has a dedicated committee responsible for assessing and monitoring the safety of medicines and vaccines, the Pharmacovigilance Risk Assessment Committee (PRAC). This ensures that EMA and the EU Member States can move very quickly once an issue is detected and take any necessary action, such as amending the information available to patients and healthcare professionals, restricting use or suspending a medicine, in a timely manner in order to protect patients.

28.4 Fast-Track Vaccine Development and Evaluation in a Public Health Emergency

CHMP can recommend the granting of MAs based on less complete data than is normally required. In such cases, the granting of an MA is subject to certain specific obligations to be reviewed annually ('conditional marketing authorization'). For example, in 2010, two pandemic influenza vaccines (H1N1), Arepanrix® and Humeza®, received conditional marketing approval. In exceptional circumstances, a MA can be granted subject to a requirement for the applicant to introduce specific procedures (safety procedures, programme of studies, prescription or administration conditions, product information), in particular, concerning the safety of the product ('marketing authorization under exceptional circumstances'). Continuation of the authorization is linked to the annual reassessment of these procedures. Imvanex®, a vaccine against smallpox, was approved in 2013 under exceptional circumstances because it had not been possible to obtain complete information about Imvanex® because of the absence of the disease.

The current pandemic demands early licensing and deployment of a vaccine against coronavirus disease 2019 (COVID-19) that provides 'worthwhile' efficacy. As large numbers of candidate drugs and vaccines for potential use in COVID-19 pandemic are being investigated, medicine regulators globally must now make urgent, informed, contextually risk-based decisions regarding clinical

trials and marketing authorizations. They must do this with the flexibility demanded by the pandemic while maintaining their core risk assessment and public safety functions.

Vaccine development for COVID-19 vaccines is being fast-tracked globally. Development is compressed in time, applying the extensive knowledge on vaccine production gained with existing vaccines. Early scientific advice from regulators helps speed up development. EMA offers to vaccine developers informal consultation with its COVID-19 Task Force (ETF), a multidisciplinary team bringing together key experts from across the European medicines regulatory network to ensure a fast and coordinated response to the pandemic. COVID-19 vaccine developers can receive prompt guidance and direction on the best methods and study designs to generate robust data. Advising companies on regulatory requirements helps ensure that standards of quality, safety, and efficacy are embedded early in the process and are not compromised by fast-track development. Vaccine manufacturers and academics use established production systems already used for safe and effective vaccines. In addition, they continuously research novel approaches to producing and developing vaccines, and some of the advances made to date are also applied to developing vaccines for COVID-19. Some vaccines for COVID-19 are developed using novel methods intended to increase the volume and speed of production compared to other types of vaccines, enhance product stability, and bring about strong immune responses.

So far COVID vaccine developers have used various approaches to reduce development timelines, such as mobilizing more human resources simultaneously to analyse results from earlier studies more quickly and map out next steps in terms of resources, funding, and regulatory strategy; combining clinical trial phases or conducting some studies in parallel where safe to do so. Companies have also expanded manufacturing capacity and large-scale production to facilitate vaccine deployment without delay once approved. In the EU, the European Commission has provided support to facilitate vaccine development and deployment as quickly as possible.

Some vaccine developers started manufacturing their COVID-19 vaccine before obtaining an EU marketing authorization. This allowed them to be ready to distribute doses rapidly enough to meet demand once they were authorized. Developers must still uphold the same good manufacturing practice (GMP) standards that apply in the EU to all vaccines. All pharmaceutical manufacturers need a manufacturing licence from the national competent authority where they operate. National competent authorities carry out GMP inspections to check that manufacturers comply with EU standards, the conditions of their licence, and the marketing authorization if obtained. The European medicines regulatory network has sped up the approval of new manufacturing lines and manufacturing sites for COVID-19 vaccines. The EU's labelling and packaging requirements are also more flexible for COVID-19 vaccines to enable rapid roll-out.

COVID-19 vaccines can only be approved and used if they comply with all the requirements of quality, safety, and efficacy set out in the EU pharmaceutical legislation. Most COVID-19 vaccines in the EU will be evaluated by EMA via the centralized procedure (which is mandatory for any vaccine using biotechnology). CHMP and PRAC carry out EMA's evaluations for COVID-19 vaccine with the help of COVID-19 ETF expertise. According to the EU pharmaceutical legislation, the standard timeline for the evaluation of a vaccine/medicine is a maximum of 210 active days. However, EMA treats marketing authorization applications for COVID-19 products in an expedited manner. This allows the timeline for evaluation to be reduced to less than 150 working days. EMA can also use its rolling review procedure for promising vaccines and medicines for COVID-19. This allows EMA to begin assessing data as they become available during the development process, to expedite the subsequent formal marketing authorization application assessment even further. When an evaluation is complete, EMA has the option of recommending a conditional marketing authorization, a type of approval for medicines addressing unmet medical needs, and in particular those to be

used in emergency situations in response to public health threats recognized by the WHO or the EU.

In the area of vaccines, it is worthwhile mentioning Article 58 of Regulation (EC) No. 726/2004, which allows the CHMP to give opinions, in co-operation with the World Health Organization (WHO), on medicinal products for human use that are intended exclusively for markets outside of the EU. Medicines eligible for this procedure are used to prevent or treat diseases of major public health interest. This includes vaccines used in the WHO Expanded Programme on Immunization for protection against a public health priority disease. The CHMP carries out a scientific assessment of applications submitted under Article 58, and, after consultation with the WHO, adopts a scientific opinion.

The requirements for the structure and content of the MAA are laid down in the EU Common Technical Document (CTD) and provide for a harmonized structure and format for MAAs in Europe, Japan, and the USA. Data generated from pharmaceutical tests, non-clinical and clinical tests and trials with the vaccine concerned, in addition to other information required by the EU legislation, need to be submitted to the EMA and all CHMP members for evaluation. The application dossier for the vaccine must be presented in accordance with the EU-CTD. The CTD is an internationally agreed format for the preparation of a well-structured application to be submitted to regulatory authorities in the three International Conference on Harmonization (ICH) regions of Europe, the USA, and Japan.

28.5 Paediatric Investigation Plans

As for all medicinal products, since 26 January 2007, vaccine developers are obliged to submit the results of studies conducted in compliance with an agreed Paediatric Investigation Plan (PIP) to have a valid application for a new MA. The Paediatric Regulation (EC) No. 1901/2006 requires the PIP to be submitted to the EMA as early as possible (ideally soon after the Phase I–II clinical trial conducted in adult populations).

The PIP describes planned clinical studies in children, including the proposed timing of the studies, formulation adaptations to make it suitable for children and non-clinical studies in juvenile animals if required. This is to ensure that the necessary data are generated determining the conditions under which the vaccine may be authorized to treat the paediatric population; in other words, a PIP should provide the data to enable the assessment of the quality, safety, and efficacy in children, and consequently the benefit–risk profile in the paediatric population. The PIP must be agreed by the EMA Paediatric Committee (PDCO) before applying for MA for any age group. The key element of the Paediatric Regulation is the early involvement of vaccine developers in the research and development programme of a medicinal product through the requirement to reach an agreement with the PDCO on the PIP. Decision on a waiver may be issued by the EMA when such paediatric development is not needed or not appropriate. Deferrals may also be granted.

The PDCO has developed a number of standard PIPs. These are documents that provide recommendations for the key binding elements to be included in the PIP opinion with the aim of assisting applicants with the agreement of PIPs on specific types or classes of medicines. A particularly challenging project was the drafting of the standard PIP for the tetanus–diphtheria pertussis (DTaP) vaccines, owing to the complexity of vaccination programmes and differences across Member States. The PDCO has defined, in collaboration with the European Centre for Disease Prevention and Control (ECDC) and European public health vaccinology experts, the schedule that should be evaluated during clinical trials in children when developing a new DTaP-containing combination vaccine. The proposed schedule has been defined as the one producing data that can cover the various vaccination schedules in the individual European Member States, through extrapolation of results to immunologically less-challenging schedules.

For vaccines and medicines for COVID-19, EMA reviews applications in an expedited manner for agreement of a PIP, deferrals or waivers and accelerates compliance checks, to speed up these products' development and approval. There are no prespecified submission deadlines and EMA's review of a PIP may take only 20 days, depending on its complexity and the applicant's preparedness to respond to questions, followed by 2 days to issue an EMA decision instead of the usual 10. Developers may provide focused scientific documentation. Compliance checks, if required, may take only 4 days.

28.6 Vaccine Development – Requirements for the MAA

28.6.1 Quality

The development of vaccines is addressed in a variety of guidelines on vaccines. There is considerable interest in developing new adjuvants for both existing and novel vaccines. The area is quite complicated and the nature and mode of action of novel adjuvants is quite wide. EU guidance on the development and regulatory approval for an adjuvant is available. An important aspect in developing a novel adjuvant is to show that it does enhance the immune response to the antigen with associated clinical benefit. The safety of novel adjuvants is also an important factor.

The quality section of an MAA requires a detailed characterization of the vaccine, a detailed description of the manufacturing process, a description of all raw materials and components used in the manufacturing process, and a description and validation of all quality control tests applied during the manufacturing process and to the vaccine itself. This section should also consider the consistency of vaccine production and the stability of the vaccine and describe an appropriate and validated potency assay for the vaccine.

There is no generic EU guideline addressing the quality requirements of vaccines; however, the requirements are similar for most biological medicinal products. Guidance is available for some specific vaccines including smallpox vaccine, influenza vaccine, recombinant viral-vectored vaccines,[16] and DNA vaccines.

28.6.2 Non-clinical

The 'Note for guidance on preclinical pharmacological and toxicological testing of vaccines' focuses on the preclinical evaluation of new vaccine products (those containing antigens not yet described in the European Pharmacopoeia monographs or in WHO requirements, or using a new conjugate for a known antigen, or any combination of known and/or new antigens). As the vaccine represents a heterogeneous class of agents, preclinical pharmacological and toxicological testing of the vaccine may be adapted for the product in question. Single-dose toxicity data from at least one animal species should be performed, with a dose providing an adequate safety margin in relation to the human dose; a study on repeated dose toxicity in one animal species for vaccines that will require multiple doses in a clinical setting is normally required. Data on reproductive function (fertility) are not usually needed, but this depends on the vaccine indication, and embryo/foetal, perinatal toxicity data, and carcinogenicity/mutagenic studies are usually not needed either. However, there are exceptions for vaccines with new adjuvants where special considerations are needed. Local tolerance should be evaluated, as vaccines are in most cases administered intramuscularly, subcutaneously, or intradermally. Immunogenicity studies look at humoral and cell-mediated response in appropriate animal models for the disease to indicate dose, schedule, and route of administration in future clinical studies. Protection studies basically establish the proof of concept of protection from disease and are established by challenge studies if feasible (e.g. ferrets challenge studies for influenza pandemic vaccines).

Secondary pharmacodynamics include safety pharmacology for the potential evaluation of undesirable pharmacological activities (the circulatory and respiratory system) and should be considered depending on the new vaccine. For vaccines protecting against infectious

diseases, not all aspects of a classical non-clinical development programme need to be covered, for example, pharmacokinetics is generally not required for vaccines. More specific non-clinical guidance is available for vaccines containing adjuvants, for smallpox vaccines, and for live recombinant viral-vectored vaccines.

28.6.3 Clinical

The EU Guideline on the clinical evaluation of vaccines provides a comprehensive explanation of the design of clinical development programmes for new vaccines that are intended to provide pre- and post-exposure prophylaxis. In the development of any new vaccine, adequate data on immunogenicity should be assembled during the clinical development programme. Aspects that should usually be covered include characterization of the immune response, investigation of an appropriate dose and primary schedule, assessment of the persistence of detectable immunity, and consideration of the need for and response to booster doses. Additionally, for vectored vaccines, the determination and characterization of the pre-existing immunity to the vector should be addressed. Pharmacokinetic studies might be required for MA when new delivery systems are used or when the vaccine contains novel adjuvants or excipients.

Ideally, protective efficacy should be performed before licensing a new vaccine. However, it is recognized that there are situations where such studies are not necessary and/or not feasible before licensing for all types of vaccines; for example, when there are established immunological correlates of protection against a specific infection such as diphtheria or tetanus or hepatitis B, immunogenicity studies may be considered sufficient. In addition, when the disease does not occur, for example, smallpox or pandemic influenza, estimating protective efficacy is not feasible.

Vaccine effectiveness reflects direct (vaccine-induced) and indirect (population-related) protection during routine use. Whether or not protective efficacy is assessed in the pre-authorization period, attempts should be made to estimate vaccine effectiveness in the post-authorization period. With the increasing complexity of vaccines and the frequent need for co-administration of multiple vaccines, immune interference has become a very important consideration.

Concerning clinical safety as pre-authorization requirements, unless otherwise justified, the recommended minimum sample size would be at least 3000 subjects for a new vaccine; the total data for pre-authorization studies should usually be sufficient to reliably determine the frequency of uncommon local and systemic adverse events, that is, frequency of 1/100 to 1/1000.

By the time a MA is granted, a risk specification should have been finalized that includes a description of possible safety issues related to the intrinsic character of the vaccine, a risk management plan (RPM) should have been agreed with the EMA, and a pharmacovigilance system (as defined in the current EU legislation) and procedures should have been put in place. The RMP defines a set of pharmacovigilance activities and interventions that identify, characterize, prevent, or minimize risks relating to the medicinal product, including the assessment of the effectiveness of those interventions. New pharmacovigilance legislation came into operation in 2012, and new provisions for Periodic Safety Update Reports (PSURs), RMPs, safety signals, and Post-Authorization Safety Studies (PASS) were introduced. In addition, literature monitoring and several tools for product safety reviews at the EU level are part of this legislation. A Pharmacovigilance Risk Assessment Committee (PRAC) has been established at the EMA, and as one of its tasks the PRAC assesses the RMP.

Considering that vaccines are almost always administered to healthy persons, the continued re-assessment of the overall risk–benefit profile has great implications.

28.7 Conclusion

Many new vaccines will become available in the very near future, which poses important challenges to the regulatory process in Europe. Large clinical trials have been carried out in the past to evaluate the efficacy and safety of vaccines, which in some cases delayed the global introduction of an important vaccine. New technologies for vaccine manufacturing have been developed that are not fully known in terms of safety and long-term efficacy. Therapeutic vaccines are becoming available for chronic diseases and it is not clear how these should be evaluated, especially in the long term. These issues require the development of a strong regulatory environment that will be able to guarantee the 'overall quality' of the new vaccines and the need for a fast and efficient process.

The current pandemic demands early licensing and deployment of a vaccine against coronavirus disease 2019 (COVID-19). As large numbers of candidate drugs and vaccines for potential use in COVID-19 pandemic are being investigated, regulators globally must now make urgent, informed, contextually risk-based decisions regarding clinical trials and marketing authorizations. The European Commission has authorized the first vaccines to prevent COVID-19 in the EU, following evaluation by EMA. EMA is liaising closely with developers of COVID-19 vaccines, mobilizing its own resources and cooperating with regulatory partners, to ensure safe and effective vaccines reach patients as soon as possible.

Further Reading

COVID-19 vaccines
https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-development-evaluation-approval-monitoring

10-year Report to the European Commission General report on the experience acquired as a result of the application of the Paediatric regulation. European Medicines Agency and its Paediatric Committee November 2016. http://ec.europa.eu/health//sites/health/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf.

COMMISSION REGULATION (EC) No 507/2006, 29 Mar 2006, Conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council.

Commission Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 Dec 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products. http://ec.europa.eu/health/files/eudralex/vol-1/reg_2010_1235/reg_2010_1235_en.pdf.

DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL 6 Nov 2001 on the Community code relating to medicinal products for human use.

Directive 2010/84/EU of the European Parliament and of the Council of 15 Dec 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. http://ec.europa.eu/health/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf and corrigendum. http://ec.europa.eu/health/files/eudralex/vol-1/dir_2010_84_cor/dir_2010_84_cor_en.pdf.

Explanatory note on immunomodulators for the guideline on adjuvants in vaccines for human use. CHMP/VWP/244894/2006. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003810.pdf.

Final paediatric investigation plan: Expected key elements and requirements for a new DTaP-containing combination vaccine for primary and booster vaccination in infants and toddlers. EMA/82701/2015. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500196478.pdf.

Guideline on adjuvants in vaccines for human use. EMEA/CHMP/VEG/134716/2004. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003809.pdf.

Guideline on clinical evaluation of new vaccines. EMEA/CHMP/VWP/164653/2005. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003870.pdf.

Guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines. EMA/CHMP/VWP/141697/2009. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/08/WC500095721.pdf.

http://ec.europa.eu/health/files/eudralex/vol-2/a/chap-4rev200604_en.pdf.

http://www.who.int/immunization/en/.

Klug B, Celis P, Ruepp R, Robertson J. Vaccines: EU regulatory requirements. Mol Vaccines. 2014;2: 845–50.

Note for guidance on cell-culture-inactivated influenza vaccines. Annex to the note for guidance on the harmonisation of requirements for influenza vaccines 2002.CPMP/BWP/2490/00. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003877.pdf.

Note for guidance on pre-clinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6). CPMP/SWP/465/95. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004004.pdf.

Note for guidance on the development of vaccinia virus-based vaccines against smallpox. CPMP/1100/02 2009. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003900.pdf.

Note for guidance on the harmonisation of requirements for influenza vaccines. CPMP/BWP/214/96 1997. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003945.pdf.

Notice to Applicants Volume 2 B – presentation and format of the dossier – Common Technical Document (CTD) May 2008. http://ec.europa.eu/health/fi les/eudralex/vol%2D%2D2/b/update_200805/ctd_05-2008_en.pdf.

Notice to Applicants Volume 2A – procedures for marketing authorisation. Chapter 4: Centralised procedure. 2016.

Points to consider on the development of live attenuated influenza vaccines 2019. EMEA/CPMP/BWP/1765/99. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003899.pdf.

REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 December 2006 on medicinal products for paediatric use.

Regulation (EC) No 726/2004 of the European Parliament and of Council, 31 Mar 2014, Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European medicines Agency. http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF

Index

H

I

J

K

L

M

N

O

P

R

S

T

U

V

W

Y