Expected and Unexpected Effects of Vaccination

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Contents

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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.

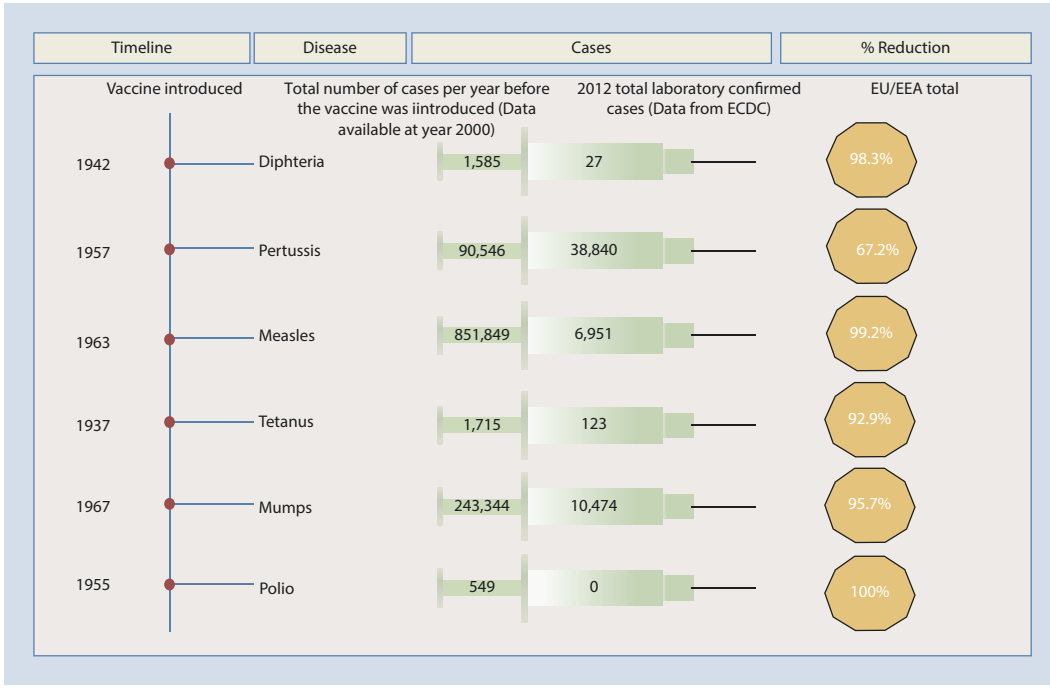

Fig. 1.1 Effectiveness and impact of the introduction of various vaccines in Europe

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,

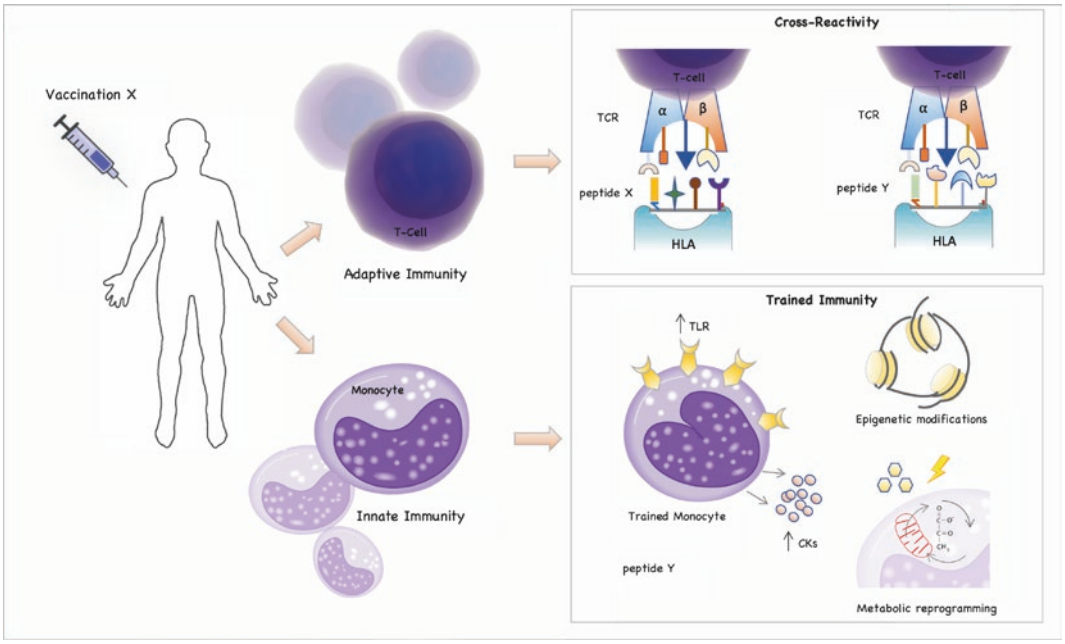

Fig. 1.2 Heterologous immunity. The concept of heterologous immunity includes both components of the immune system: Adaptive T cells can recognize cross-reactive peptides by alternative recognition of TCR, and "trained" monocytes of innate system respond more efficiently to a non-related peptide in a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

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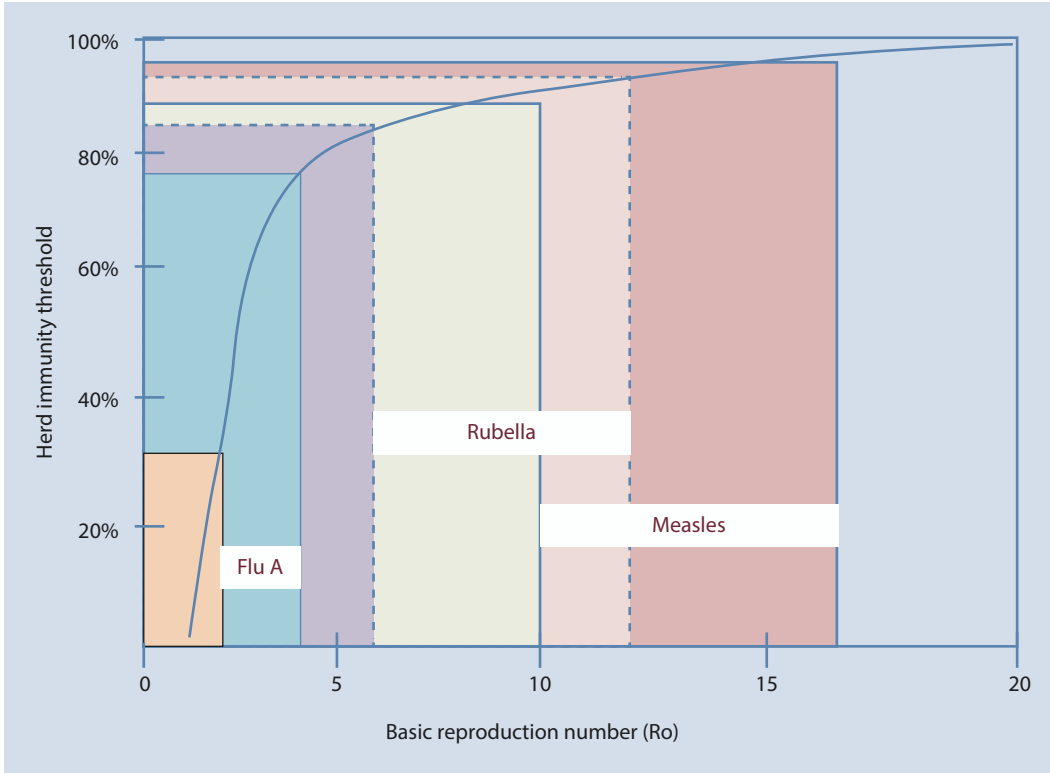

Fig. 1.3 Simple threshold concept of herd immunity. Relationship between the herd immunity threshold, $(R_0 - 1)/R_0 = 1 - 1/R_0$, and basic reproduction number, R_0, in a randomly mixing homogeneous population. Note the implications of ranges of R_0, which can vary considerably between populations,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

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