Practical Issues in Geriatrics
Series Editor: Stefania Maggi

Jean-Pierre Michel
Stefania Maggi *Editors*

Adult Vaccinations

Changing the Immunization Paradigm

Springer

Practical Issues in Geriatrics

Series Editor
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Padua
Italy

This practically oriented series presents state of the art knowledge on the principal diseases encountered in older persons and addresses all aspects of management, including current multidisciplinary diagnostic and therapeutic approaches. It is intended as an educational tool that will enhance the everyday clinical practice of both young geriatricians and residents and also assist other specialists who deal with aged patients. Each volume is designed to provide comprehensive information on the topic that it covers, and whenever appropriate the text is complemented by additional material of high educational and practical value, including informative video-clips, standardized diagnostic flow charts and descriptive clinical cases. Practical Issues in Geriatrics will be of value to the scientific and professional community worldwide, improving understanding of the many clinical and social issues in Geriatrics and assisting in the delivery of optimal clinical care.

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ISSN 2509-6060 ISSN 2509-6079 (electronic)
Practical Issues in Geriatrics
ISBN 978-3-030-05158-7 ISBN 978-3-030-05159-4 (eBook)
https://doi.org/10.1007/978-3-030-05159-4

Library of Congress Control Number: 2019930438

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

Foreword

Adult Vaccinations: Essential But Too Often Forgotten

The European Interdisciplinary Council on Ageing (EICA) is a European platform fostering interdisciplinary analysis, high-level discussion as well as translation and dissemination of results from ageing research to various professional groups, policy makers, and the general public. The EICA was founded by an active group of geriatricians and gerontologists from the European Union Geriatric Medicine Society (EUGMS), and social scientists active in the Survey of Health, Ageing and Retirement in Europe (SHARE), with the informal support of the European Partnership of Active Health Ageing. The EICA has its headquarters on the island of San Servolo, Venice, at Venice International University, and its main aims included building on, and making use of existing European and international expertise in the field of ageing, promoting an interdisciplinary focus on questions relating to ageing, health and care; acting as a non-partisan, independent and not-for-profit organisation, remaining open to all scientifically and politically engaged persons and institutions interested by the field of ageing research. To achieve these aims, EICA board members and consultants actively identify highly relevant questions and challenges facing the field of ageing and ageing research, for European individuals, healthcare professionals and policy makers. One of its main activities is the development and organisation of interdisciplinary Master Classes on Ageing, geriatric medicine and gerontology, to update healthcare professionals' knowledge of this growing field. Secondly, it is the role of EICA to release European position papers and reports with a view to fostering knowledge transfer towards the general public and lay persons. Finally, and most importantly for this book, the EICA also organizes interprofessional conferences for scientists, policy-makers, healthcare providers, hospital operators, insurance companies, the medical and pharmaceutical industry, and other stakeholders directly or indirectly impacted by issues related to ageing.

In this context, from 24 to 26 May 2017, the EICA and the EUGMS jointly organized a conference entitled "Changing the vaccine paradigm: Stressing the importance of adult immunization", in San Servolo, Venice, Italy. This meeting fits perfectly with the WHO concept of healthy ageing, which is the "process of developing and maintaining the functional ability that enables well-being in older age". Indeed, rather than focusing on the absence of disease, healthy ageing is a concept

that should be considered from the perspective of functional ability, which enables older people to be, and to do, what they have reason to value. The WHO has identified four major pillars underpinning the promotion of health and the prevention of disease over the life course, and these are nutrition, physical activity, smoking cessation, and vaccination.

In this context, the specific objectives of this meeting on adult vaccination were to review vaccine preventable diseases and vaccine performance in older adults, analyse the impact of adult vaccination programmes currently adopted in Europe, and understand the challenges to greater vaccine uptake in the general population, particularly vaccine scepticism, among the public, the media and even medical practitioners, since Europe has the dubious honour of being world leader in terms of vaccine hesitancy. Indeed, adult vaccination is a key step to preserving good health among the adult population as they move towards and into older age, but policies are heterogeneous across countries, and the utility of adult vaccination is not always given due consideration in public health policy. The multidisciplinary audience of the meeting should help to produce a comprehensive multi-step, coherent action plan for the future to help overcome hesitancy and scepticism regarding vaccination of older adults in Europe, and support recommendations from scientific societies.

A wide range of high-quality presentations during the meeting provided background information on available vaccines, vaccination programmes throughout Europe and the world, the efficacy of specific vaccines in various patient populations, as well as broader perspectives, such as the "One Health" concept, reminding us that human health should be considered within the wider context of all living organisms. Finally, group discussions between experts from a range of disciplines analysed existing obstacles to adult vaccination, and put forward propositions to establish a successful global vaccine policy. The summaries of all these presentations are presented here, and provide a comprehensive and well-documented basis for the evaluation of adult vaccination and life-course vaccination policy in the world today.

We hope that these foundations will lay the path towards more uniform vaccination policies, and decisive action to improve vaccine uptake in adults around the world, a major step towards improving well-being in older age for future generations.

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Contents

Complexity of Vaccine Manufacture and Supply

1

Philippe Juvin

Vaccination is recognized as one of the most successful and cost-effective public health interventions ever introduced. However, in the world today, there is a shortage of medicines and vaccines on the global scale. This situation is widely recognized by regulators, politicians and the industry and has been a major subject of debate widely publicized in the medical literature [1–4]. In May 2016, addressing the global shortage of medicines and vaccines featured as a prominent item on the agenda of the 69th World Health Assembly, which urged its member states "to develop strategies that may be used to forecast, avert or reduce shortages/stockouts" [5]. Indeed, ensuring a continuous supply of high-quality, safe, effective and affordable medicines is a fundamental component of a good health system, and shortages in medication supply can jeopardize the principle of equal access for everyone, everywhere, to enjoy the highest possible standard of health [5].

In this context, challenging public health situations have been reported in several countries around the world, in particular shortages of paediatric doses of therapies for diseases such as HIV and tuberculosis [6]. The production of drugs and vaccines is a complex journey within a highly regulated industry, with the result that changes or incidents anywhere along that journey may affect production capacity and supply chains at the end of the road. There are certain specificities that are characteristic of biological products such as vaccines. Drug substances are produced as a result of operations performed in a multitude of semi- or (ideally) fully dedicated manufacturing buildings or equipment, including facilities dedicated to medium preparation, inactivation, viral growth or antigen purification, amongst others. Thus, the production of vaccines of consistently high quality requires specialized equipment, long and complex manufacturing cycles, in an increasingly regulated environment.

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_1

1.1 The Complex Journey of a Vaccine

The first step in vaccine production is the reception of the raw material, which must be compliant with stringent quality specifications. Once the raw materials are received, the antigen, i.e. the active ingredient of the vaccine, is manufactured in bulk, in the most critical step in the production process. Paediatric vaccines may contain from one to nine antigens, all of which must be produced separately. Then, the active ingredient is mixed with the other ingredients that will ensure an immune response and guarantee product stability. Next, the vaccine is filled into its final container, 100% visually inspected, packaged and labelled in accordance with regulatory requirements. The vaccine is now ready for shipping to the customer, but quality controls must first be performed, and once successful, the national regulatory authority in the country where the vaccine is to be distributed gives the final authorization for the product to be released [7]. A cycle of production for a vaccine can last from 6 to 29 months, which implies that vaccines received in pharmacies today may have started production up to 3 years ago. Throughout this time, between 100 and more than 1000 quality control tests are performed. Indeed, it is estimated that around 70% of the manufacturing time is dedicated to quality control.

In view of the complexity of this lengthy process, it is hard to establish inventories of what vaccines are available, and where, or when they may become available. This is compounded by the long manufacturing cycles and biological variability, and the short shelf life (1–3 years), which starts to countdown from the formulation step of the manufacturing process. In addition, industrial production capacity may be slow to grow in response to increased demand in such a highly regulated environment.

In this context, the pharmaceutical industry is making a concerted effort to improve vaccine availability, in concertation with other major stakeholders, such as governments, wholesalers, regulators and the pharmacy profession. Within the industry, pharmaceutical companies continue to develop the competencies and expertise of their vaccine production teams, to ensure that cutting-edge sciences continue to be translated into vaccine solutions for the general public. They also strive to increase production capacity and modernize production processes and analytical test methods to ensure optimal efficiency along the production process. Continual improvements are being made to the pharmaceutical quality system, taking country-specific requirements into account at all steps. In addition, pharmaceutical companies inform health authorities of potential supply disruptions, engage in active dialogue with health authorities and regulatory agencies to enhance sustainability of vaccine supply and work towards reducing the complexity and constraints of the regulatory process.

The worldwide demand for vaccines is extremely unpredictable, and rapid modulations can be required in response to multiple factors. Stock-outs may occur, although these are not always necessarily related to shortages in supply, since procurement problems, ineffective management and national financial considerations may also be involved. Also, in response to pandemics or more local health alerts,

there may be unexpected peaks in demand for certain vaccines, whereas the production capacity may have not have the ability to upscale in a sufficiently timely manner. In response to the H1N1 influenza pandemic of 2009, over 78 million doses of vaccine were distributed to over 70 countries, but unfortunately, it has been reproached that many of these arrived after the potential for achieving maximum effect had passed [8]. This problem is being partially addressed by initiatives such as the mechanism established in 2016 by WHO, Médecins Sans Frontières, UNICEF and Save the Children, in discussion with vaccine manufacturers, to facilitate access to affordable vaccines in humanitarian emergencies. The so-called Humanitarian Mechanism was launched in May 2017 and has already been called upon several times to accelerate access to affordable vaccines in crisis situations [9].

Post-approval changes to vaccines represent another major challenge to vaccine production and supply. Most major pharmaceutical companies are globalized, and ideally, each product would be produced in a single version for worldwide distribution. However, the reality is somewhat different. Regulatory approvals and procedures are mainly nationalized, with each country having specific requirements that need to be applied for marketing authorization of the vaccine in that country. Therefore, the ideal single product becomes, in reality, a single product with over 100 different approvals. Obtaining approval in each individual country is time-consuming, and procedures are not harmonized between countries, with the result that review times vary widely, particularly if different countries consider the same change to be of varying degrees of importance. For example, what is considered a minor change in one country may be considered as a major change in another country, thus involving more complex review. If the manufacturer decides to make a change to the product (or if such a change is mandated by health authorities), it may take up to 5 years between the receipt of approval from the first and the last country. This is not only a challenge to consistent supply but is also a barrier to technological innovation and continued improvement. For example, for a single pentavalent vaccine containing 8 antigens, there may be 83 batches and 55 processes in a single year, while at the same time, many other "versions" of the product can be stocked in inventory, thus making logistics a considerable challenge. In addition, any variation occurring in a vaccine will have a ripple-down effect along the production process, since each component of the vaccine in turn has its own manufacturing processes. Changes may include quality improvements to the vaccine itself, changes to the labelling, changes to quality control or mandatory changes to meet new regulatory standards. Once the new vaccine (or version thereof) is planned for release, and the regulatory approvals are ongoing, the manufacturer may downscale, not to say stop production, but as long as the new vaccine is still not fully approved and being distributed, there is a "vulnerable" time period during which there may be potential for a shortfall in supply, especially if demand increases abruptly due to external factors. Clearly, in the face of vaccine demand that may fluctuate rapidly, regulatory processes for post-approval changes have a considerable impact on vaccine supply, availability and equity of access.

A further conundrum for vaccine supply is independent batch release. Manufacturers perform several hundred in-company quality control tests using

validated methods before a vaccine batch is released. However, dual testing is systematically performed, by Official Medical Control Laboratories, which support regulatory authorities in controlling the quality of medicinal products available on the market, independently from the manufacturers. These Official Medical Control Laboratories perform tests, many of which are the same as those already performed by the manufacturer. This dual testing can delay the release and, thus, lead to shorter batch shelf lives. The number of national control laboratories has risen from around 20 countries in 2006 to over 60 countries in 2014, thus considerably complicating the batch release process.

While keeping high-quality vaccines as a prerequisite, vaccine manufacturers are implementing several strategies to reduce the extent of national control laboratory testing and, thereby, reduce the complexity of the batch release process. Firstly, they strive to raise awareness, by communicating about the risk to supply and the unnecessary repetition of tests. Suggested elements of an action plan for a sustainable global improvement include replacing some tests by in vitro methods, standardization of pharmacopeias, obtaining reliance and mutual recognition between countries and reward systems for consistently high-performing and reliable suppliers. The potential public health benefits include a marked reduction of the manufacturing cycle time, cost savings due to less testing and more reliable supply of vaccines for the consumer.

In summary, the production of consistently high-quality and effective vaccines is a long and complex process. The environment is highly regulated, yet with variations in the applicable regulations between countries. In addition, there is a multitude of production phases, in a range of production sites, globalized logistics for stocking and distribution and unpredictable demand from the world population, resulting in potential for shortages on a global scale. Introducing new products or changes to existing products requires extensive research and time-consuming regulatory approvals that may also jeopardize the flow of vaccine supply. A platform for open and continuous dialogue between public health institutions and industry is warranted to discuss strategies for decreasing the complexity of vaccine production and release, as well as reducing the regulatory burden of post-approval changes. All stakeholders must seek common solutions for improved vaccine supply, have better anticipation of vaccine needs, encourage innovation and ultimately improve vaccine availability, guaranteeing equal access to high-quality vaccines for all.

References

1. Gatesman ML, Smith TJ. The shortage of essential chemotherapy drugs in the United States. N Engl J Med. 2011;365(18):1653–5.
2. Chabner BA. Drug shortages—a critical challenge for the generic-drug market. N Engl J Med. 2011;365(23):2147–9.
3. Jensen V, Rappaport BA. The reality of drug shortages—the case of the injectable agent propofol. N Engl J Med. 2010;363(9):806–7.
4. Mirtallo JM. The drug shortage crisis. JPEN J Parenter Enteral Nutr. 2011;35(4):433.

5. Sixty-ninth World Health Assembly. Addressing the global shortage of medicines and vaccines. WHA69.25. 2016. http://apps.who.int/medicinedocs/documents/s22423en/s22423en.pdf. Accessed 23 June 2018.
6. Waning B, Diedrichsen E, Jambert E, Barnighausen T, Li Y, Pouw M, et al. The global pediatric antiretroviral market: analyses of product availability and utilization reveal challenges for development of pediatric formulations and HIV/AIDS treatment in children. BMC Pediatr. 2010;10:74.
7. International Federation of Pharmaceutical Manufacturers & Associations. The complex journey of a vaccine. The manufacturing chain, regulatory requirements and vaccine availability. 2016. https://www.ifpma.org/wp-content/uploads/2016/01/TheComplexJourneyofaVaccinePRINT-EN.pdf. Accessed 23 June 2018.
8. Fineberg HV. Pandemic preparedness and response—lessons from the H1N1 influenza of 2009. N Engl J Med. 2014;370(14):1335–42.
9. World Health Organization. Vaccination in humanitarian emergencies: implementation guide. Geneva. Licence: CC BY-NC-SA 3.0 IGO. 2017. http://www.who.int/immunization/documents/general/who_ivb_17.13/en/. Accessed 23 June 2018.

2 Administration of Vaccines: Current Process, New Technologies and Adjuvants

Giuseppe Del Giudice and Alberta Di Pasquale

The benefits of vaccination, particularly in the paediatric context, are undeniable, and there have been huge reductions in childhood infectious diseases. Indeed, this success has a certain downside, namely, it is likely that many doctors nowadays would not even recognize a case of diphtheria or measles. The impact of systematic immunization in the paediatric population is substantial, with reductions of over 95% in the number of reported cases of such diseases as diphtheria, measles or polio [1]. To arrive at their current situation of widespread use, vaccine formulations and administration have travelled a long path since the first vaccines were developed against smallpox more than two centuries ago. Today, most vaccines are still given by injection, and very few are administered via the oral, intranasal or intradermal route; however, progress in pharmaceutical science over the same period has taught us a lot about tailoring vaccine formulations and routes for administration in order to obtain effective immune responses.

Logically, many expect to see the same benefits observed for paediatric vaccines in the older adult population; however, there is an age-related decline in immune function that impacts their ability to respond to infections and to vaccines. It is known that innate immunity is paramount in activating adaptive immunity and that information innate cells received after an infection or after a vaccination shapes the signals and pathways that will be provided to T and B cells in the lymph nodes. For example, it is known that age-related changes in T-cell function are associated with decreased immunogenicity and efficacy of influenza vaccine in older adults [2, 3]. Research has indicated that older adults have an altered balance of memory CD4+ T cells, which potentially affects long-term CD4+ T-cell responses to the influenza vaccine [4]. Similarly, in response to vaccination against hepatitis B virus, it has

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_2

been reported that the formation of antibodies in response to vaccination was significantly reduced among older subjects (from 50 years of age) compared with their younger counterparts (from 18 years of age) [5]. Finally, with regard to vaccination with polysaccharide vaccines for the prevention of adult disease from *Streptococcus pneumoniae*, Schenkein et al. reported that although adults of all ages produced similar concentrations of antibodies in response to pneumococcal vaccines, the antibodies they produced had significantly reduced functionality [6]. Consequently, the response to infection and vaccination are significantly impaired in the older adults, and specialized solutions are therefore needed to achieve better vaccine immunogenicity and efficacy among these populations.

A further obstacle is that vaccination coverage is not optimal. The fact that a vaccine exists is no guarantee that it is administered to the target group. Several reasons contribute to low vaccine coverage, including ethnic differences, lack of awareness among both the public and healthcare providers, failure of the healthcare provider to recommend vaccination and lack of systematic assessment of vaccination status at each medical visit. Other considerations such as reimbursement, lack of national recommendations for vaccination and stock-outs at local level may also enter into play. Importantly, perception of efficacy of the vaccine may be a big contributor to acceptance and, thereby, coverage. Based on a sample of >36,000 adults aged ≥19 years from the 2014 NIHS, vaccination coverage rates among those aged 65 years and over were 71.5% for influenza, 61.3% for pneumococcal vaccination coverage and 57.7% for tetanus [7].

Given that vaccine effectiveness may be lower among those who are most in need of immunity, such as older adults, and given that coverage is suboptimal, the question arises as to how mortality and morbidity from the disease will progress in scenarios with low or no vaccination. Taking the case of influenza vaccine as an example, a meta-analysis including 17 randomized controlled trials and 14 observational studies reported a pooled vaccine effectiveness of 59% (95% CI 51–67) against influenza confirmed by RT-PCR or viral culture in healthy adults aged <65 years [8]. Among older adults (aged 65 years and older), effectiveness is reportedly lower, at only 40–60% [9]. Nevertheless, vaccination has an impact on severe disease. In Italy, in the 2014–2015 season, there was low influenza vaccine coverage after a few batches of the vaccine were put on hold due to safety concerns that were later confirmed as unfounded. The resulting mortality and morbidity from influenza due to this reduced vaccination rate were similar to those observed during the 2009 H1N1 pandemic where the majority of the population was naïve to the new pandemic strain [10]. Similarly, in Sweden, after the withdrawal of the DTPw (diphtheria/tetanus/whole-cell pertussis) vaccine in 1979, the incidence of pertussis rose considerably in Sweden as compared with neighbouring country Norway, to reach comparable to those of some developing countries [11–13]. Finally, in an ongoing measles outbreak in Italy, with over 4400 cases reported in 20 regions from January to August 2017, 88% of the cases occurred in unvaccinated individuals [14]. Therefore, high coverage is essential to maintain health in the population, and there is value in using even those vaccines that appear less than optimal since the impact of vaccination is still substantial in terms of death and hospitalization avoided.

How can we work towards better immunization performance? Firstly, by guaranteeing high coverage and herd immunity in the population that will help protect unvaccinated individuals; secondly, by working on formulations with higher antigen content; or thirdly, by developing alternative delivery routes, or different adjuvants, i.e. substance able to enhance the immune response to vaccine antigens.

Herd immunity is beneficial when the right population is targeted, namely, those individuals who are high transmitters of disease; in the case of influenza, these are often children [15]. Japan had a long history of vaccinating schoolchildren against influenza, achieving up to 85% annual coverage among children up to 15 years of age. However, this programme was discontinued in 1994 due to safety scares and also misclassification of influenza; as a consequence of the interruption of children vaccination, mortality in older adults started to increase again to the point that the Japanese Ministry of Health decided to switch flu vaccination to older adults (aged 65 years and older) and those aged 60–64 with concomitant high-risk conditions in order to reduce it. A detailed comparison of age-specific influenza-related excess mortality rates in Japanese seniors aged ≥65 years during (1978–1994) and after the vaccination programme (1995–2006) found that schoolchildren vaccination was associated with a 36% adjusted mortality reduction among Japanese seniors (95%CI, 17–51%), corresponding to around 1000 senior deaths averted annually by vaccination of schoolchildren (95%CI, 400–1800) [16]. Therefore, protection of potential carriers and disease transmitters in the population is vital in contributing to prevention of disease among the unvaccinated and immunocompromised.

Intradermal administration of vaccines has generated a lot of research since the derma is rich of Langerhans cells that are very efficient as antigen-presenting cells. Researches on this route of administration so far have done variable results in particular due to the difficulty to reach the derma with classical syringes; in fact the intradermal administration is possible only by using specific devices. However, in some vaccines (e.g., rabies, influenza), the intradermal route has been demonstrated as a feasible approach being pursued by some groups. Those vaccines administered by the intradermal route have been shown to be comparable to intramuscular/subcutaneous vaccines in terms of immunogenicity, safety, reactogenicity and tolerability and preferred by patients who are scared of needles [17, 18].

In addition to research into new administration routes, several new technologies are being developed in the last 10 years, such as reverse vaccinology and novel adjuvants, synthetic biology and structural vaccinology. One important aspect in this technological quest is the time required to discover new vaccine antigens and to prove their efficacy and safety in clinical trials. Reverse vaccinology helps to address this challenge by using whole-genome sequences to identify potential antigens likely to induce protective antibodies and then working backwards from the antigen towards a vaccine. This approach allows for the rapid identification of promising vaccine candidates that may never have been discovered by traditional means. Reverse vaccinology was successfully applied to develop the vaccine against group B meningococcus [19] and continues to be applied to other diseases in the hope of accelerating new vaccine development.

The speed of development of vaccines is a major factor in containing epidemics of emerging diseases. In today's world of non-stop intercontinental air travel, viruses spread very rapidly throughout the planet, in a pattern that defies prediction. During the 2009 H1N1 pandemic, the response in terms of vaccine preparation was the fastest ever, but it was still too slow to contain the epidemic. Indeed, from 12 April 2009 to 10 April 2010, it is estimated that approximately 60.8 million cases and 12,469 deaths occurred in the United States due to H1N1 [20], but the vaccine only became available in substantial quantities during the second pandemic peak [21]. Consequently, close to 40% of cases occurred during a time when no vaccine was available, thus hampering the potential benefit of vaccination in containing the epidemic. Progress in synthetic biology shows hope for the future. When a potential deadly outbreak of H7N9 influenza emerged in China in 2013, the sequence was released on 31 March by the Chinese CDC, and only 6 days later, the virus was rescued in the cell line; thus, in 1 week, the virus was available by coding sequencing and synthesizing appropriate genes, assembling and sending the material to the US Centre for Disease Control, and a vaccine became possible [22, 23]. This technology might significantly shorten the time to availability of a vaccine and represents a major step forwards in pandemic preparedness. This is also important as it may change availability of vaccines for use in the general population. Indeed, in view of the large numbers of constantly emerging and re-emerging diseases, new systems need to be developed that can help to accelerate response to public health emergencies.

A final area that has been the focus of intense research in recent years concerns novel vaccine adjuvants. Aluminium salts, introduced in the 1920s, are the most commonly used adjuvants in the majority of vaccines. A period of more than 70 years elapsed before new adjuvants were approved, in Italy and Europe, namely, MF59 and then AS03, AS04 and AS01. The use of adjuvants in vaccines has several beneficial effects, including increased and persistent T-cell and antibody response [24–28], an antigen dose-sparing effect [29–31], increased breadth of the antibody response with MF59 and AS03 adjuvants [32, 33], as well as evidence of cross-reactivity in T-cell response [34–36]. Efficacy data show enhanced efficacy with adjuvanted vaccines in children [37], while a prospective, observational study of over 170,000 persons-seasons of observation from Northern Italy also showed enhanced effectiveness, with a 25% reduction in the risk of hospitalization for influenza or pneumonia (relative risk 0.75, 95% CI 0.57–0.98) [38]. With regard to herpes zoster, primary infection with varicella zoster virus induces T-cell immune memory, and this immunity may be periodically boosted by exposure to varicella or by silence reactivation from latency. Varicella zoster virus-specific memory T cells decline with age, and in specific conditions of immune impairment, herpes zoster thus frequently reactivates in older adults or immunosuppressed individuals. In this way, it was possible to formulate and develop a subunit vaccine against zoster, using as antigen the protein gE, which has an essential functional role in viral infection and is expressed on the surface of infected cells and is a target of both humoral and cellular responses [39–41]. The adjuvant AS01, used in the vaccine, was selected based on preclinical evaluation and previous clinical experience and

comprises a unique combination of immune stimulants such as MPL and saponin, QS-21, on a liposome basis, enhancing cellular response. Strikingly, and unexpectedly, with the adjuvant AS01, one of the mechanisms of immune response was observed to be due to NK cells, activated immediately after immunization. Indeed, within hours after injection of the AS01-adjuvanted vaccine, resident cells, such as NK cells, release IFNγ in the lymph node draining the injection site, in a reaction found to be essential for the further activation of additional dendritic cells and the development of cell-mediated immunity [42]. Accordingly, the adjuvant AS01 was shown to be efficient at promoting CD4+ T-cell-mediated immune responses and shows how adjuvants can trigger natural pathways and enhance the efficacy of vaccines. This has the potential to achieve major benefits among individuals who have a reduced intrinsic capacity to respond, such as the older adults and the immunocompromised.

In conclusion, vaccines have a long history of efficacy and tolerability, but coverage rates remain suboptimal, and this can hamper effectiveness and impact of vaccination as a public health strategy. Vaccine uptake can be increased by conveying the message to healthcare providers and the populations that vaccines are important. In addition, considering the herd immunity effect of vaccinating large cohorts of individuals, reaching and maintaining high coverage remain necessary to ensure that the full benefits of immunization are achieved even with suboptimal vaccines. Reduced coverage can lead to reappearance of severe infections. Targeting the right population for vaccination and achieving sufficient coverage rates help protect non-vaccinated or immunocompromised groups. New technologies are revolutionizing the field of vaccine development; their ability to make possible new and more effective vaccines will further increase benefits of vaccinations in the years to come.

Acknowledgements This work was sponsored by GlaxoSmithKline Biologicals SA. Giuseppe Del Giudice and Alberta Di Pasquale are employees of the GSK Group of Companies.

References

1. World Health Organization. Global and regional immunization profile: European region. 2017. http://www.who.int/immunization/monitoring_surveillance/data/gs_eurprofile.pdf?ua=1. Accessed 24 June 2018.
2. Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. Vaccine. 2006;24(8):1159–69.
3. Simonsen L, Taylor RJ, Viboud C, Miller MA, Jackson LA. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. Lancet Infect Dis. 2007;7(10):658–66.
4. Kang I, Hong MS, Nolasco H, Park SH, Dan JM, Choi JY, et al. Age-associated change in the frequency of memory CD4+ T cells impairs long term CD4+ T cell responses to influenza vaccine. J Immunol. 2004;173(1):673–81.
5. Rosenberg C, Bovin NV, Bram LV, Flyvbjerg E, Erlandsen M, Vorup-Jensen T, et al. Age is an important determinant in humoral and T cell responses to immunization with hepatitis B surface antigen. Hum Vaccin Immunother. 2013;9(7):1466–76.
6. Schenkein JG, Park S, Nahm MH. Pneumococcal vaccination in older adults induces antibodies with low opsonic capacity and reduced antibody potency. Vaccine. 2008;26(43):5521–6.

7. Williams WW, Lu PJ, O'Halloran A, Kim DK, Grohskopf LA, Pilishvili T, et al. Surveillance of vaccination coverage among adult populations—United States, 2014. MMWR Surveill Summ. 2016;65(1):1–36.
8. 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(1):36–44.
9. McElhaney JE. Influenza vaccination in the elderly: seeking new correlates of protection and improved vaccines. Aging Health. 2008;4(6):603–13.
10. Istituto Superiore di Sanita. Seasonal influenza 2014–2015. Epidemiological surveillance. 2015. http://old.iss.it/binary/iflu/cont/Influnet_stagione_2014_2015.pdf. Accessed 15 Aug 2018.
11. Gangarosa EJ, Galazka AM, Wolfe CR, Phillips LM, Gangarosa RE, Miller E, et al. Impact of anti-vaccine movements on pertussis control: the untold story. Lancet. 1998;351(9099):356–61.
12. Romanus V, Jonsell R, Bergquist SO. Pertussis in Sweden after the cessation of general immunization in 1979. Pediatr Infect Dis J. 1987;6(4):364–71.
13. Galazka A. Control of pertussis in the world. World Health Stat Q. 1992;45(2–3):238–47.
14. Filia A, Bella A, Del Manso M, Baggieri M, Magurano F, Rota MC. Ongoing outbreak with well over 4,000 measles cases in Italy from January to end August 2017—what is making elimination so difficult? Euro Surveill. 2017;22(37):30614.
15. Halloran ME, Longini IM Jr. Public health. Community studies for vaccinating schoolchildren against influenza. Science. 2006;311(5761):615–6.
16. Charu V, Viboud C, Simonsen L, Sturm-Ramirez K, Shinjoh M, Chowell G, et al. Influenza-related mortality trends in Japanese and American seniors: evidence for the indirect mortality benefits of vaccinating schoolchildren. PLoS One. 2011;6(11):e26282.
17. Bragazzi NL, Orsi A, Ansaldi F, Gasparini R, Icardi G. Fluzone(R) intra-dermal (Intanza(R)/Istivac(R) Intra-dermal): an updated overview. Hum Vaccin Immunother. 2016;12(10):2616–27.
18. Robertson CA, Tsang P, Landolfi VA, Greenberg DP. Fluzone(R) Intradermal Quadrivalent Influenza Vaccine. Expert Rev Vaccines. 2016;15(10):1245–53.
19. Parikh SR, Andrews NJ, Beebeejaun K, Campbell H, Ribeiro S, Ward C, et al. Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study. Lancet. 2016;388(10061):2775–82.
20. Shrestha SS, Swerdlow DL, Borse RH, Prabhu VS, Finelli L, Atkins CY, et al. Estimating the burden of 2009 pandemic influenza A (H1N1) in the United States (April 2009–April 2010). Clin Infect Dis. 2011;52(Suppl 1):S75–82.
21. Tizzoni M, Bajardi P, Poletto C, Ramasco JJ, Balcan D, Goncalves B, et al. Real-time numerical forecast of global epidemic spreading: case study of 2009 A/H1N1pdm. BMC Med. 2012;10:165.
22. Bart SA, Hohenboken M, Della Cioppa G, Narasimhan V, Dormitzer PR, Kanesa-Thasan N. A cell culture-derived MF59-adjuvanted pandemic A/H7N9 vaccine is immunogenic in adults. Sci Transl Med. 2014;6(234):234ra55.
23. Dormitzer PR, Suphaphiphat P, Gibson DG, Wentworth DE, Stockwell TB, Algire MA, et al. Synthetic generation of influenza vaccine viruses for rapid response to pandemics. Sci Transl Med. 2013;5(185):185ra68.
24. Galli G, Hancock K, Hoschler K, DeVos J, Praus M, Bardelli M, et al. Fast rise of broadly cross-reactive antibodies after boosting long-lived human memory B cells primed by an MF59 adjuvanted prepandemic vaccine. Proc Natl Acad Sci U S A. 2009;106(19):7962–7.
25. Galli G, Medini D, Borgogni E, Zedda L, Bardelli M, Malzone C, et al. Adjuvanted H5N1 vaccine induces early CD4+ T cell response that predicts long-term persistence of protective antibody levels. Proc Natl Acad Sci U S A. 2009;106(10):3877–82.
26. Leroux-Roels G, Bourguignon P, Willekens J, Janssens M, Clement F, Didierlaurent AM, et al. Immunogenicity and safety of a booster dose of an investigational adjuvanted polyprotein HIV-1 vaccine in healthy adults and effect of administration of chloroquine. Clin Vaccine Immunol. 2014;21(3):302–11.
27. Leroux-Roels G, Van Belle P, Vandepapeliere P, Horsmans Y, Janssens M, Carletti I, et al. Vaccine Adjuvant Systems containing monophosphoryl lipid A and QS-21 induce strong

humoral and cellular immune responses against hepatitis B surface antigen which persist for at least 4 years after vaccination. Vaccine. 2015;33(8):1084–91.
28. Leroux-Roels I, Devaster JM, Leroux-Roels G, Verlant V, Henckaerts I, Moris P, et al. Adjuvant system AS02V enhances humoral and cellular immune responses to pneumococcal protein PhtD vaccine in healthy young and older adults: randomised, controlled trials. Vaccine. 2015;33(4):577–84.
29. Baras B, Stittelaar KJ, Simon JH, Thoolen RJ, Mossman SP, Pistoor FH, et al. Cross-protection against lethal H5N1 challenge in ferrets with an adjuvanted pandemic influenza vaccine. PLoS One. 2008;3(1):e1401.
30. Leroux-Roels I, Borkowski A, Vanwolleghem T, Drame M, Clement F, Hons E, et al. Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine: a randomised controlled trial. Lancet. 2007;370(9587):580–9.
31. Nolan T, Roy-Ghanta S, Montellano M, Weckx L, Ulloa-Gutierrez R, Lazcano-Ponce E, et al. Relative efficacy of AS03-adjuvanted pandemic influenza A(H1N1) vaccine in children: results of a controlled, randomized efficacy trial. J Infect Dis. 2014;210(4):545–57.
32. Khurana S, Verma N, Yewdell JW, Hilbert AK, Castellino F, Lattanzi M, et al. MF59 adjuvant enhances diversity and affinity of antibody-mediated immune response to pandemic influenza vaccines. Sci Transl Med. 2011;3(85):85ra48.
33. van der Most RG, Roman FP, Innis B, Hanon E, Vaughn DW, Gillard P, et al. Seeking help: B cells adapting to flu variability. Sci Transl Med. 2014;6(246):246ps8.
34. Einstein MH, Baron M, Levin MJ, Chatterjee A, Fox B, Scholar S, et al. Comparison of the immunogenicity of the human papillomavirus (HPV)-16/18 vaccine and the HPV-6/11/16/18 vaccine for oncogenic non-vaccine types HPV-31 and HPV-45 in healthy women aged 18–45 years. Hum Vaccin. 2011;7(12):1359–73.
35. Einstein MH, Baron M, Levin MJ, Chatterjee A, Fox B, Scholar S, et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 vaccine and HPV-6/11/16/18 vaccine: follow-up from months 12–24 in a Phase III randomized study of healthy women aged 18–45 years. Hum Vaccin. 2011;7(12):1343–58.
36. Moris P, van der Most R, Leroux-Roels I, Clement F, Drame M, Hanon E, et al. H5N1 influenza vaccine formulated with AS03 A induces strong cross-reactive and polyfunctional CD4 T-cell responses. J Clin Immunol. 2011;31(3):443–54.
37. Vesikari T, Knuf M, Wutzler P, Karvonen A, Kieninger-Baum D, Schmitt HJ, et al. Oil-in-water emulsion adjuvant with influenza vaccine in young children. N Engl J Med. 2011;365(15):1406–16.
38. Mannino S, Villa M, Apolone G, Weiss NS, Groth N, Aquino I, et al. Effectiveness of adjuvanted influenza vaccination in elderly subjects in northern Italy. Am J Epidemiol. 2012;176(6):527–33.
39. Berarducci B, Ikoma M, Stamatis S, Sommer M, Grose C, Arvin AM. Essential functions of the unique N-terminal region of the varicella-zoster virus glycoprotein E ectodomain in viral replication and in the pathogenesis of skin infection. J Virol. 2006;80(19):9481–96.
40. Berarducci B, Rajamani J, Reichelt M, Sommer M, Zerboni L, Arvin AM. Deletion of the first cysteine-rich region of the varicella-zoster virus glycoprotein E ectodomain abolishes the gE and gI interaction and differentially affects cell-cell spread and viral entry. J Virol. 2009;83(1):228–40.
41. Malavige GN, Jones L, Black AP, Ogg GS. Varicella zoster virus glycoprotein E-specific CD4+ T cells show evidence of recent activation and effector differentiation, consistent with frequent exposure to replicative cycle antigens in healthy immune donors. Clin Exp Immunol. 2008;152(3):522–31.
42. Coccia M, Collignon C, Herve C, Chalon A, Welsby I, Detienne S, et al. Cellular and molecular synergy in AS01-adjuvanted vaccines results in an early IFNgamma response promoting vaccine immunogenicity. NPJ Vaccines. 2017;2:25.

3 How Can the European Medicines Agency Support an Appropriate Strategy of Adult Vaccination?

Francesca Cerreta

Like all regulatory agencies, the European Medicines Agency (EMA) has a legal mandate, and its actions are enshrined in law. The mandate of the EMA includes authorisation of vaccines; risk management of vaccines (post-authorisation data collection and risk minimisation); collection of safety data, for example, through notification of adverse drug reactions; and post-authorisation safety and efficacy studies. Indeed, in the framework of post-authorisation safety and efficacy, the EMA has the power to impose certain studies on drug companies and/or to evaluate clinical protocols and results. The EMA's remit further includes monitoring the risk-benefit balance of vaccines, and if anomalies are observed or adverse events arise, regulatory action may be taken, ranging from request of further studies to changes to the marketing authorization and, in rare cases, to suspension or revocation of the marketing authorisation. Finally, the EMA also has a commitment to transparency, with the obligation to maintain a database of all products on the European Union (EU) market, the publication of clinical trials data and involvement of expert groups including academics to contribute to the assessment process.

In practice, what does that mean? The job of a good regulator is to ask the right questions and to provide support to help find the right answers, because assumptions lead to evidence-bias, not evidence base. In the case of vaccines in particular, the right questions include: what population will use the vaccine? Is the benefit/risk ratio supported for that population? Is there is a currently neglected population that will benefit from the vaccine? What are the knowledge gaps and how can we address them? And are there areas of unmet medical need?

Gaps in existing knowledge can be addressed by various mechanisms: first among these methods is by ensuring that trials reflect the at-risk population, so EMA encourage enrollment of patients at risk. Second, knowledge gaps can be addressed by providing appropriate specific guidance, for example, regarding

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_3

immunogenicity, immunosenescence or inclusion of a representative sample. A third method is the implementation of a comprehensive risk management plan (RMP). Part of the approval process for a drug is the safety specification. This is characterised by the identification of what is known and what is not known about the drug, the target population and the disease itself. For the drug, for example, data such as pharmacodynamics, pharmacokinetics, how it will be used, the adverse event profile, class effects, potential interactions and the level of confidence need to be detailed. Regarding the target population, it is important to identify what patients or subjects were studied, what types of patient/subject were not studied, what the potential risk factors are and what events can be expected in this population. Lastly, the nature of the disease, including its natural history and epidemiology, and the events that occur in the course of its natural progression need to be taken into account. This information leads to the compilation of a list of important identified and potential risks as well as missing information that needs to be investigated. Then, it becomes possible to identify and characterise safety concerns and formulate a pharmacovigilance plan, which comprises routine activities (such as collection of adverse drug reactions, follow-up questionnaires, signal detection, annual reports, literature reviews), plus a range of additional activities, covering areas such as active surveillance, registries, record linkage, case-control or cohort studies, drug utilisation studies or post-authorisation clinical trials, through to assessment of the effectiveness of risk minimisation measures.

Indeed, in terms of population-level vaccination policies, the guidelines for good pharmacovigilance practice stipulate the need for risk minimisation, which encompasses both prevention and minimisation of risk. Routine strategies to minimise risk at a regulatory level include ensuring the adequacy of the legal status of the product, the pack size, the summary of product characteristics, the package leaflet and the labelling. Further actions to minimise risk include educational programmes for healthcare professionals and patients, checklists or algorithms for prescription or controlled access.

Influenza (flu) vaccine effectiveness (VE) studies are a good example of this process in action. Such studies are included in the risk management plan, and for the flu vaccine, continuous VE monitoring is necessary to the change in vaccine composition from year to year. VE studies include the collection of brand-specific data, in line with guidelines for good epidemiological practice and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Companies must liaise with organisations, institutions and public health authorities who have experience in influenza pharmacovigilance and who have implemented a functioning infrastructure to conduct multicentre studies. Results must be collected from different seasons before conclusions can be drawn, and regulatory actions may then be considered if a specific concern is identified or strongly suspected by the deviation of the results from the expected pattern.

The fourth and final means to address knowledge gaps is to define unmet needs within the EU and to foster research. In Europe, several major topics are currently the focus of the EMA's attention, including immunosenescence, nosocomial infections, pneumococcal disease, and herpes zoster. Recent guidelines have been issued

on diseases of interest, while collaborative actions are also helpful, such as the FDA/Health Canada cluster on clostridium and synergies with the industry and academic, like the BioVacSafe (BioVacSafe.eu) initiative to accelerate and improve the testing and monitoring of vaccine safety, both before and after release to the market. Catch-up vaccination of migrants from countries where there is no childhood vaccine programme is another important and topical issue in Europe at the current time.

Multilateral collaboration is key to help identify unmet needs on a global scale, and also to improve understanding about how a given vaccine actually performs in clinical practice, to inform any future recommendations and to ensure that they can truly be implemented. To this end, the EMA maintains regular and open discussions with various stakeholders, including public health institutes and centres for disease control, national health authorities, marketing authorisation holders, institutions or foundations as well as research organisations.

In conclusion, as regards the EMA's role in supporting or enabling appropriate adult vaccination strategies, there is strong attention at European level into the safety, efficacy, effectiveness and risk-benefit ratios of vaccines in the older population. Public health authorities play a key role in the collection of data, and all stakeholders must have clearly defined roles and responsibilities, not only at a national level but striving for a consolidated and uniform approach. Funding models that support synergies between industry and public are desirable, however there is a trade-off between the need for reliable and useful data and the cost, of obtaining that data: the burden must be commensurate to the usefulness. The EMA remains firmly committed to a collaborative approach, in terms of both technical and governance issues. Finally, the EMA will continue to explore valid suggestions (target diseases, biomarkers, improvement of reporting) to fulfil these important objectives.

4 Public Health Impact of Adult Vaccine-Preventable Diseases on Performance, Disability, Mortality and Healthcare Costs in Europe

Giovanni Rezza

As we move well into the twenty-first century, people are living to increasingly older ages, and there is a worldwide increase in the proportion of older people. As a consequence of this population ageing phenomenon, it is perfectly natural that we will need to prevent diseases among these elders, in line with the adult vaccination paradigm. This perspective raises two major questions. Firstly, are vaccine-preventable diseases (VPDs) a public health problem in adults and the elderly, warranting systematic vaccination, and if yes, what is the evidence in support of this posit? Secondly, is there really a need to vaccinate older adults and will it be beneficial?

It is now clearly established that the effect of immunisation in a community goes beyond simply the target group of vaccination. Indeed, the level of protection in one age group modifies the level of protection in another age group through an indirect effect. The vaccination strategy applied to vaccinate a specific target group (i.e. epidemic amplifiers such as school children) modifies the epidemiology of a disease in all age groups (i.e. in the elderly). This needs to be taken into consideration when considering the possible vaccination of older age groups. Infectious diseases continue to spread because of insufficient herd immunity, which is due to low vaccination coverage among children (e.g. measles), or germ circulation among adolescents and older age groups (e.g. *Neisseria meningitidis*). A high proportion of adults do not acquire immunity through natural infection with several biological agents, and even in those who have acquired immunity, protection does not last forever, as immunity wanes with increasing age. Therefore, there is likely a need for direct protection of adults, especially older adults, through vaccination.

In Italy, a new vaccination calendar has been introduced with the intent to offer an immunisation plan from birth to old age, thus encompassing recommendations

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_4

for older individuals. This plan was initiated on foot of pressure from scientific societies that advocated for a lifelong vaccination calendar.

VPDs in the elderly mainly comprise the "cursed triad" of influenza (flu), pneumococcal pneumonia, and herpes zoster. The flu vaccine is the most widely used vaccine in Europe, and most countries have programmes to protect older individuals against flu. All EU member states recommend the vaccine for those aged over 65 years, and the majority also fund it. Influenza is also the only case where a specific Council Recommendation for the vaccination of older age groups exists at EU level and with a specific target for coverage (75% vaccine coverage rate, VCR). Unfortunately, accurate figures are lacking about the true magnitude of flu infection rates, although it is estimated to affect 5–15% of the population, corresponding to 35–110 million (average 70 million) persons, with around 94,000 excess deaths directly or indirectly attributable and 50,000 excess hospitalisations.

The European Mortality Monitoring Project (EuroMOMO) is a routine public health mortality monitoring system aimed at detecting and measuring, on a real-time basis, excess number of deaths related to influenza and other possible public health threats across participating European countries. Data from the EuroMOMO project illustrate that every 2 years, there is a high peak, with excess mortality observed every year, although this is an indirect estimate of mortality attributable to flu. Overall, target groups for flu vaccination represent 36% of the EU population, amounting to approximately 180 million persons eligible for vaccination, while the elderly account for 48% of all target groups [1]. Vaccine coverage varies widely across countries, and although good coverage rates, at around 60%, were observed up to a few years ago, these have since been decreasing and may now be less than 50%. This may be partially explained by the limitations to flu vaccination among the elderly. For example, there is a higher impact of H3 strains compared to H1 strains, and there is also a paucity of clinical trials of flu vaccines among the elderly. Furthermore, effectiveness may be low due to a mismatch between the strain and the vaccine. Possible advantages with the use of adjuvanted vaccines deserve to be explored.

Pneumococcal vaccination is also spreading in Europe, although recommendations, funding opportunities and age thresholds for vaccination vary widely across member states. Lower respiratory infections are the fourth most common cause of death worldwide, especially in the elderly, and in 2013, pneumococcal pneumonia was the leading known cause of lower respiratory infection mortality, causing approximately 22% of lower respiratory infection deaths [2]. There is a wealth of reliable data in the literature regarding the incidence of community-acquired pneumonia (CAP) in Europe, which is estimated to range from 1.07 to 1.2 per 1000 person-years overall [3], and increases with age [3, 4] and comorbidities [5, 6]. In a prospective Spanish cohort study that included 11,240 individuals aged 65 years or older, followed from January 2002 to April 2005 for primary endpoints of all-cause CAP and 30-day mortality after diagnosis, incidence was found to increase dramatically with age and was also doubled in men as compared to women [7]. Similarly, a prospective observational cohort study conducted over 2 years in a large teaching hospital trust in the United Kingdom reported 30-day mortality of

10% for all-cause CAP, with almost 40% having pneumococcal pneumonia [8]. Indeed, *Streptococcus pneumoniae* is the most frequently isolated pathogen in CAP within the hospital, ICU and outpatient settings [9, 10], underlining that these cases are for the large part preventable. Trends in the notification rate of cases of invasive pneumococcal disease have been decreasing slowly and slightly in all age groups over the last few years, but incidence remains high in older groups, and the decline is very gradual despite vaccination strategies in some countries [11]. The risk of pneumococcal pneumonia increases with age and in the presence of comorbidities. Data from a retrospective cohort study from three large, longitudinal, US healthcare databases of medical and outpatient pharmacy claims from 2007 to 2010 reported significant increases in the rate ratios for pneumococcal pneumonia in patients with comorbid conditions, ranging from a rate ratio of 2.8 for those diabetes compared to healthy subjects to 3.8 to chronic heart disease, 3.9 for smokers, 5.9 in patients with asthma and 7.9 in those with chronic lung disease [12]. Not only do these conditions favour the development of CAP, but in patients who get infected with CAP, existing diseases may worsen. Indeed, a survey using a specifically designed questionnaire among 500 participants with a CAP diagnosis confirmed by chest imaging in the past 120 days reported at least 1 illness-related impact on their daily life and activities from CAP, with over three quarters of respondents (77.4%) reporting the needed assistance during their bout of pneumonia [13]. In the longer term, pneumococcal pneumonia is also associated with poorer long-term survival. In an American study of 392 patients (mean age 63, 98% men) with pneumococcal pneumonia followed up for 10 years, the death rate appeared to be far greater among 1-month survivors of pneumococcal pneumonia than among the general population of American men of the same age [14]. This underscores the fact that the deleterious effects of pneumococcal pneumonia remain perceptible long after the acute episode is over. In this regard, the case fatality rate for pneumococcal pneumonia has not changed significantly in the last few decades, consistently being reported in the range of 11.5 to 12.3%, from 1996 to 2009, in a wide mix of patient populations from different settings and countries [15–18]. This important fact needs to be taken into account when considering implementation of vaccination programmes.

The third and final member of the "cursed triad" is herpes zoster (HZ). Few European countries provide and/or fund national vaccination programmes for HZ. The risk of HZ and post-herpetic neuralgia increases with age, with two thirds of cases occurring in adults aged over 50. Cell-mediated immunity to the varicella zoster virus decreases with increasing age, and people with chronic diseases such as chronic obstructive pulmonary disease, diabetes or cardiovascular disease are particularly susceptible [19]. Available data from Europe indicate that annual HZ incidence is relatively stable, ranging from 2.0 to 4.6/1000 person-years overall, but increasing rapidly after the age of 50 years to around 7 to 8/1000 person-years and up to 10/1000 person-years after 80 years of age [20]. Up to 20% of those affected by HZ may subsequently suffer post-herpetic neuralgia, accounting for more than 250,000 cases per year [21]. Hospitalisation is common, with longer length of stay in older patients, who have a mean length of stay of around 8 days, which is long

and thus costly [22]. In anticipation of the possible introduction of an immunisation programme for the elderly in Tuscany, the burden of disease caused by HZ and its complications was assessed through a retrospective analysis of 4475 hospital admissions between 2002 and 2012 [23]. Over the 10-year period, the authors reported that most hospitalisations (68%) were subjects aged over 65 years and the mean length of stay was 9.5 days. Almost half the patients (48.5%) had no complications, while among those with complications, the most frequent were neurological (24.2%) and ophthalmic (16.5%) [23]. At an average annual cost of 1,261,544 euro overall, and 3101 euro per hospitalised case [23], there is clearly potential for major savings through vaccination in this context.

In addition to the "cursed triad" of diseases, childhood diseases that are preventable by vaccination, such as measles, tetanus and pertussis, should not be forgotten, as several among them have recently been on the rise in adults. Indeed, childhood VPDs do not only affect children, but it is not rare for adults to be infected also. Data from the World Health Organization indicate that there was an outbreak of measles in Italy in 2016, with 866 reported cases of measles, representing an increase of almost two-and-a-half times compared to 2015 (259 cases) [24]. One third of those affected were adults (>30 years of age), in whom complications are common, including hospitalisation in almost 40%, pointing to a cost-benefit ratio clearly in favour of vaccination.

Similarly, pertussis is also common among adults, especially women, and may in turn be a source of infection for neonates. Diphtheria and tetanus are also common, and despite initial vaccination, immunity tends to wane as many subjects tend to forget the boosters. A review of statutory notification, hospitalisation, mortality and seroprevalence data to describe tetanus epidemiology in Italy from 2001 to 2010 reported a total of 594 tetanus cases, with an average annual incidence of 1.0/1000,000 population [25]. Among these, 80% of cases occurred in subjects aged >64 years and more frequently in women. The death rate and burden of disease in this completely preventable disease suggest that vaccine boosters are largely overlooked and there is room for significant improvement in vaccine and booster uptake for tetanus.

Overall, there are many challenges to vaccination against VPDs in adults. Despite different policies and disease prevalence across countries, several issues remain common to all stakeholders. Firstly, the epidemiology of diseases varies between countries, so a "one-size-fits-all" policy may not be the most suitable. Second, adult migrants may increase this variability. Thirdly, evidence regarding the burden of VPDs may not be available at a national level in every country, which may hamper policy implementation efforts in individual countries. Finally, immunisation schedules need to be adapted at a national level to cater for local conditions and cultures, and programmes for adult vaccination should be monitored using the same standards as those applied to childhood vaccination programmes, in order to assess their impact and effectiveness.

In conclusion, the world population is increasingly older, with ever more comorbidities. The burden of VPDs is therefore all the more relevant, even for diseases that are traditionally rare in adulthood, such as measles. Although scientific

evidence is not always sufficient to convince policymakers to adopt appropriate preventive strategies, adult vaccination should be considered as a key priority and advocated by health authorities and stakeholders worldwide for the years to come.

References

1. Preaud E, Durand L, Macabeo B, Farkas N, Sloesen B, Palache A, et al. Annual public health and economic benefits of seasonal influenza vaccination: a European estimate. BMC Public Health. 2014;14:813.
2. GBD Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117–71.
3. Torres A, Peetermans WE, Viegi G, Blasi F. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. Thorax. 2013;68(11):1057–65.
4. Vila-Corcoles A, Ochoa-Gondar O, Rodriguez-Blanco T, Raga-Luria X, Gomez-Bertomeu F, Group ES. Epidemiology of community-acquired pneumonia in older adults: a population-based study. Respir Med. 2009;103(2):309–16.
5. Benard A, Mercie P, Alioum A, Bonnet F, Lazaro E, Dupon M, et al. Bacterial pneumonia among HIV-infected patients: decreased risk after tobacco smoking cessation. ANRS CO3 Aquitaine Cohort, 2000–2007. PLoS One. 2010;5(1):e8896.
6. Mullerova H, Chigbo C, Hagan GW, Woodhead MA, Miravitlles M, Davis KJ, et al. The natural history of community-acquired pneumonia in COPD patients: a population database analysis. Respir Med. 2012;106(8):1124–33.
7. Ochoa-Gondar O, Vila-Corcoles A, de Diego C, Arija V, Maxenchs M, Grive M, et al. The burden of community-acquired pneumonia in the elderly: the Spanish EVAN-65 study. BMC Public Health. 2008;8:222.
8. Bewick T, Sheppard C, Greenwood S, Slack M, Trotter C, George R, et al. Serotype prevalence in adults hospitalised with pneumococcal non-invasive community-acquired pneumonia. Thorax. 2012;67(6):540–5.
9. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax. 2012;67(1):71–9.
10. Lode HM. Managing community-acquired pneumonia: a European perspective. Respir Med. 2007;101(9):1864–73.
11. European Centre for Disease Prevention and Control. Annual Epidemiological Report 2016—invasive pneumococcal disease. Stockholm. 2016. http://ecdc.europa.eu/en/healthtopics/invasivepneumococcaldisease/Pages/Annualepidemiologicalreport2016.aspx. Accessed 9 Jan 2018.
12. Shea KM, Edelsberg J, Weycker D, Farkouh RA, Strutton DR, Pelton SI. Rates of pneumococcal disease in adults with chronic medical conditions. Open Forum Infect Dis. 2014;1(1):ofu024.
13. Wyrwich KW, Yu H, Sato R, Strutton D, Powers JH. Community-acquired pneumonia: symptoms and burden of illness at diagnosis among US adults aged 50 years and older. Patient. 2013;6(2):125–34.
14. Sandvall B, Rueda AM, Musher DM. Long-term survival following pneumococcal pneumonia. Clin Infect Dis. 2013;56(8):1145–6.
15. Fine MJ, Smith MA, Carson CA, Mutha SS, Sankey SS, Weissfeld LA, et al. Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. JAMA. 1996;275(2):134–41.
16. Feikin DR, Schuchat A, Kolczak M, Barrett NL, Harrison LH, Lefkowitz L, et al. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995–1997. Am J Public Health. 2000;90(2):223–9.
17. Restrepo MI, Mortensen EM, Velez JA, Frei C, Anzueto A. A comparative study of community-acquired pneumonia patients admitted to the ward and the ICU. Chest. 2008;133(3):610–7.

18. Klausen HH, Petersen J, Lindhardt T, Bandholm T, Hendriksen C, Kehlet H, et al. Outcomes in elderly Danish citizens admitted with community-acquired pneumonia. Regional differences, in a public healthcare system. Respir Med. 2012;106(12):1778–87.
19. Burke BL, Steele RW, Beard OW, Wood JS, Cain TD, Marmer DJ. Immune responses to varicella-zoster in the aged. Arch Intern Med. 1982;142(2):291–3.
20. Pinchinat S, Cebrian-Cuenca AM, Bricout H, Johnson RW. Similar herpes zoster incidence across Europe: results from a systematic literature review. BMC Infect Dis. 2013;13:170.
21. Johnson RW, Wasner G, Saddier P, Baron R. Postherpetic neuralgia: epidemiology, pathophysiology and management. Expert Rev Neurother. 2007;7(11):1581–95.
22. Gabutti G, Serenelli C, Cavallaro A, Ragni P. Herpes zoster associated hospital admissions in Italy: review of the hospital discharge forms. Int J Environ Res Public Health. 2009;6(9):2344–53.
23. Levi M, Bellini I, Capecchi L, Pieri L, Bechini A, Boccalini S, et al. The burden of disease of Herpes Zoster in Tuscany. Hum Vaccin Immunother. 2015;11(1):185–91.
24. World Health Organisation. A report on the epidemiology of selected vaccine-preventable diseases in the European Region. WHO EpiBrief. 2017;1:1–12.
25. Filia A, Bella A, von Hunolstein C, Pinto A, Alfarone G, Declich S, et al. Tetanus in Italy 2001–2010: a continuing threat in older adults. Vaccine. 2014;32(6):639–44.

Outcomes After HPV Vaccination

5

Xavier Bosch José

Human papillomavirus (HPV) is a small, non-enveloped, double-stranded DNA virus of the *Papillomaviridae* family. This family contains hundreds of different viruses, in a wide range of hosts in both animals and humans, and at least 13 types are known to be oncogenic, i.e. responsible for cervical and other anogenital and oropharyngeal cancers. Since it was first causally implicated in the development of cervical cancer over 30 years ago, a large body of evidence has accumulated substantiating the causal role of certain high-risk subtypes of HPV [1]. HPV types 16 and 18 are known to cause about 70% of all cases of invasive cervical cancer worldwide [2], with type 16 reportedly having the greatest oncogenic potential, while low-risk HPV genotypes 6 and 11 are reported to be responsible for around 90% of cases of anogenital warts [3].

Over 600,000 new cases of anogenital and oropharyngeal cancers per year, accounting for 5% of all cancers, can be attributed to HPV infection, including virtually all cases of cervical cancer and 88% of anal cancers [4]. Indeed, cervical cancer is the first cancer to be recognized by the WHO as being 100% attributable to an infectious agent [5].

A review and synthetic analysis estimating the number of cancer cases attributed to infection in 2008 reported that among an estimated 12.7 million new cancers worldwide, around 2 million were attributable to infections, corresponding to 16.5% of cancer cases [6]. HPV was responsible for an estimated 610,000 cases worldwide (30% of all infection-attributable cancers), of which 490,000 occurred in less developed regions and the remaining 120,000 in more developed regions [6]. Cervical cancer accounted for half of all attributable cases in women. There were an

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_5

estimated 311,365 deaths from cervical cancer worldwide in 2018, accounting for 7.5% of all female cancer deaths, and almost 6 out of 10 (59.4%) cervical cancer deaths occur in low and low-middle income regions [7].

HPV exclusively infects epithelial cells and exploits the differentiation pathway of epithelial cells to replicate itself; there is no viraemia. The virus penetrates the epithelium through microabrasions and infects the epithelial stem cells located in the basal layer of the epithelium. It does not cross the basement membrane and, as a result, escapes detection by the immune system. It also remains in the epithelium, and so, natural infection does not confer long-term protection against reinfection. The virus infects the basal layer stem cells and uses host cells to replicate viral DNA and express virally encoded proteins, delaying cell cycle arrest and normal differentiation [8]. This in turn allows further viral replication. Virus-encoded structural proteins L1 and L2 are expressed in the most superficial layers of the epithelium, assembled in the cell nucleus, and ultimately, new infectious virions are released with the cells as they are shed from the epithelial surface [4, 8].

Since persistent (>5 years) HPV infection with one of the high-risk genotypes has been proven to be a prerequisite for the development of HPV-related cancers [8, 9], prophylactic vaccines have been developed in recent years to prevent the future development of cancer or its precursors. The vaccines are prepared from purified L1 structural proteins and work by forming HPV type-specific virus-like particles (VLPs) that block interaction with the basal layer receptor, thus reducing the number of cells that are infected after challenge with the virus, which in turn contributes to preventing clinical disease. The vaccines contain no live biological products or viral DNA and, thus, do not cause active infection. Currently, three different vaccines are commercially available (Table 5.1), covering up to nine different HPV types. Although other HPV types are not currently included in marketed vaccines, there is such a wide array that the cost of including them in vaccines largely outweighs the potential benefit to be gained, thus making it unrealistic in the current context to expand vaccination to these types. Indeed, the 9-valent vaccine currently on the market covers up to 90% of the cancer-causing HPV types, and in a randomized trial, efficacy in terms of the rate of high-grade cervical, vulvar, or vaginal disease related to the five additional oncogenic types included in the 9-valent vaccine was 96.7% (95% confidence interval, 80.9–99.8) [10]. In addition, antibody

Table 5.1 Human papillomavirus vaccines available as of May 2018

	Bivalent	Quadrivalent	Nine-valent
Trade name	Cervarix®	Gardasil®	Gardasil-9®
Manufacturer	GlaxoSmithKline	Merck Sharp & Dohme	Merck Sharp & Dohme
HPV genotypes	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Adjuvant	AS04: 500 μg aluminium hydroxide, 50 μg 3-deacylated monophosphoryl lipid A (MPL)	225 μg amorphous aluminium hydroxyl-phosphate sulphate	500 μg amorphous aluminium hydroxyl-phosphate sulphate

responses to HPV-6, HPV-11, HPV-16, and HPV-18 were noninferior to those generated by the quadrivalent vaccine [10].

Since HPV vaccination first started to be included in national vaccination policies in 2006, when the quadrivalent HPV vaccine was introduced in the USA and in Sweden, there have been a large number of publications reporting evidence of the significant positive impact of vaccination on genital warts, cervical abnormalities, and HPV prevalence. In a report from Australia, where free quadrivalent HPV vaccines were provided to girls aged 12–18 and women up to 26 years of age, free of charge, from mid-2007 to 2009, Read et al. reported the near disappearance of genital warts among young women with a decline from 18.6% to 1.9% in women under 21, accompanied by a corresponding decrease in heterosexual men aged under 21 years from 22.9% to 2.9%, even though men were not vaccinated [11]. In a meta-analysis of 20 studies undertaken in 9 high-income countries, representing more than 140 million person-years of follow-up, Drolet et al. reported that in countries with HPV vaccination coverage of at least 50% among women, infections with HPV types 16 and 18 decreased significantly between the pre- and postvaccination periods by 68% (relative risk (RR) 0.32, 95% CI 0.19–0.52) [12]. There was also a significant reduction in HPV types 31, 33, and 45 in the same age group, suggesting cross-protection, while there was also evidence of herd protection with significant reductions in anogenital warts in boys younger than 20 years of age and in women aged 20–39 years [12]. Interestingly, in countries where female vaccination coverage was lower than 50%, significant reductions in HPV type 16 and 18 infection (RR 0.50, [95% CI 0.34–0.74]) and in anogenital warts (0.86 [95% CI 0.79–0.94]) were seen in girls aged less than 20 years, but there was no evidence of cross-protection or herd effects [12].

In line with the findings in terms of HPV infections, there is a large body of evidence in support of the effectiveness of HPV vaccination against cervical abnormalities. Data from Victorian Cervical Cytology Registry in the state of Victoria, Australia, show that declines are now being observed in the rate of high-grade cervical abnormalities in the 25–29-year age group, with the first suggestion of a downturn in the long-term slow increase in rates in the 30–34-year-old age group, since the introduction of HPV vaccination among adolescent girls [13, 14]. The oldest women vaccinated as adult women as part of the catch-up programme in Australia are now 35 years old, so this suggests that new infection and disease are now being prevented in this population also, even though they may have had prevalent infection at the time of vaccination [13, 14]. Follow-up through a population-based cancer registry of two Finnish vaccination trial cohorts and unvaccinated controls demonstrated that HPV vaccination had sustained protective effectiveness against cervical intraepithelial neoplasia grade 3, irrespective of HPV type, at 10 years post-vaccination [15, 16]. This beneficial effect has recently been confirmed to extend to invasive cancer, in a report of follow-up of these same cohorts of HPV-vaccinated and HPV-unvaccinated females originally aged 14–19 years [17]. This is the first evidence that HPV vaccination provides protection against invasive cervical cancer and is a fundamental argument underpinning the need to continue and expand implementation of vaccination programmes in young women.

5.1 Future Prospects

Overall, to date, over 100,000 subjects have received HPV vaccines in randomized trials, and in routine practice, over 240 million doses of HPV vaccine have been distributed, with an estimated 60 million persons vaccinated. There have been 8 reviews by the WHO of HPV vaccine safety in over 60 countries, of which 30 are in Europe, which have introduced routine HPV vaccination, including a growing number of countries that also vaccinate males. The results are overwhelmingly in favour of vaccination programmes and their efficacy against HPV-induced infections as well as against cervical cancer and its precursors. Side effects from vaccination are minor and infrequent. In this context, it is clear that there is sufficient compelling evidence to recommend that vaccination of girls must continue and expand (i.e. to two-dose regimes). Vaccination of boys, already started in some countries, also deserves to be extended, while studies are ongoing regarding the utility of HPV vaccination in middle-aged women and high-risk groups. Finally, the WHO is considering including cervical cancer among the diseases that could be eliminated by intelligent combinations of vaccination and screening, which would indeed represent a huge step forward in terms of public health around the world, ensuring highly effective and evidence-based protection for future generations.

References

1. Malik H, Khan FH, Ahsan H. Human papillomavirus: current status and issues of vaccination. Arch Virol. 2014;159:199–205.
2. Arbyn M, Xu L, Simoens C, et al. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Database Syst Rev. 2018;5:CD009069.
3. World Health Organization. Human papillomavirus vaccines WHO position paper. Wkly Epidemiol Rec. 2009;85:118–31. http://www.who.int/wer/2009/wer8415.pdf. Accessed 27 May 2018.
4. Crosbie EJ, Einstein MH, Franceschi S, et al. Human papillomavirus and cervical cancer. Lancet. 2013;382:889–99.
5. Bosch FX, Lorincz A, Munoz N, et al. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol. 2002;55:244–65.
6. de Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012;13:607–15.
7. International Agency for Research on Cancer (IARC). GLOBOCAN 2018: cervical cancer estimated incidence, mortality and prevalence worldwide in 2018. 2018. http://gco.iarc.fr/today/explore. Accessed 27 December 2018.
8. Frazer IH. Prevention of cervical cancer through papillomavirus vaccination. Nat Rev Immunol. 2004;4:46–54.
9. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189:12–9.
10. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015;372:711–23.
11. Read TR, Hocking JS, Chen MY, et al. The near disappearance of genital warts in young women 4 years after commencing a national human papillomavirus (HPV) vaccination programme. Sex Transm Infect. 2011;87:544–7.

12. Drolet M, Benard E, Boily MC, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis. 2015;15:565–80.
13. Brotherton JM, Winch KL, Bicknell L, et al. HPV vaccine coverage is increasing in Australia. Med J Aust. 2017;206:262.
14. Brotherton JM, Gertig DM, May C, et al. HPV vaccine impact in Australian women: ready for an HPV-based screening program. Med J Aust. 2016;204:184–e1.
15. Rana MM, Huhtala H, Apter D, et al. Understanding long-term protection of human papillomavirus vaccination against cervical carcinoma: cancer registry-based follow-up. Int J Cancer. 2013;132:2833–8.
16. Lehtinen M, Lagheden C, Luostarinen T, et al. Ten-year follow-up of human papillomavirus vaccine efficacy against the most stringent cervical neoplasia end-point-registry-based follow-up of three cohorts from randomized trials. BMJ Open. 2017;e015867:7.
17. Luostarinen T, Apter D, Dillner J, et al. Vaccination protects against invasive HPV-associated cancers. Int J Cancer. 2018;142:2186–7.

Impact of Nutrition on Adult Vaccination Efficacy

6

Claudio Franceschi and Aurelia Santoro

A reported 2–10% of patients fail to mount a response to routine vaccines, and non-responsiveness increases with age, and in particular, vaccination to a novel vaccine in persons aged older than 65 years is associated with a high rate of low or non-responsiveness [1]. This conundrum poses a problem for immunologists, leading to the posit that to improve the efficacy of vaccination, not only chronological age but also biological age should be considered. Indeed, certain parameters that are markers of chronological age show increased variance with older age, and thus, certain individuals can have a marker level that matches the expected level for their age in the population or the level of a younger age group (i.e. biological age may be lower than chronological age) or the level of an older age group (i.e. biological age may be higher than chronological age) [2]. Epigenetic research has also helped to shed light on the determinants of ageing. The epigenome is the intermediate layer of genomic information between the genome and transcriptome. Using data from more than 8000 samples present in 82 DNA methylation array datasets encompassing 51 healthy tissues and cell types, obtained by Illumina platforms (Infinium 450 K and 27 K), Horvath et al. identified in the whole genome 353 CpG sites whose methylation level is a multi-tissue predictor of age, making it possible to estimate epigenetic age versus chronological age, namely, the DNA methylation age (DNAm age) [3]. This age predictor was shown to have good predictive accuracy in most tissue and cell types, with a correlation of 0.97 with chronological age and a median error of 2.9 years [3]. Applying this multi-tissue predictor to semi-supercentenarians (subjects who have reached the age of 105–109 years), Horvath et al. found in a study of 82 Italian semi-supercentenarians (mean age 105 years) that their offspring (mean age 71.8 ± 7.8 years) had a lower epigenetic age than age-matched controls (average age difference 5.1 years) [4]. Thus, the rate of ageing appears to be decelerated in the super-old and in their offspring, while accelerated epigenetic ageing has been

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_6

demonstrated to occur in Down syndrome, for example, suggesting that trisomy 21 represents a model of accelerated ageing [5].

Further insights into the processes involved in ageing come from the field of glycomics. N-glycans profiling appears to be one of the most robust biomarkers of biological age. Recently developed high-throughput methods of analysis have enable investigation of the whole spectrum of N-linked glycans (N-glycome) in a large number of individuals, revealing characteristic ageing-associated N-glycome changes reminiscent of those associated with inflammatory and autoimmune diseases [6]. Recent data suggest that the N-glycomic shift observed in ageing may be related not only to inflammation but also to alteration of important metabolic pathways. In this way, N-glycans are not only powerful markers of ageing but also possibly contribute to its pathogenesis [6]. There is also evidence that strong correlations exist between glycomics and functional, haematological, immunological, inflammatory and metabolic variables, particularly with C-reactive protein, insulin and body mass index. An analysis of the N-glycome in 76 Down syndrome persons, 37 siblings and 42 mothers of Down syndrome persons identified specific glycomic changes associated with Down syndrome, ageing in Down syndrome, as well as ageing in controls, identifying glycomic features in line with accelerated ageing in Down syndrome [7].

HIV is also considered as a model of accelerated ageing. To establish whether HIV disease was associated with abnormal levels of age-related brain atrophy, Cole et al. used neuroimaging data from HIV-positive and HIV-negative individuals to estimate brain-predicted age difference, i.e. brain-predicted age—chronological age [8]. They observed that HIV-positive individuals showed increased brain-predicted age difference scores, compared to HIV-negative individuals. Mean brain-predicted age difference score in HIV-positive individuals was 2.15 ± 7.8 years, while in HIV-negative individuals it was −0.87 ± 8.4 years. Brain-predicted age significantly positively correlated with chronological age in both groups. They also observed lower brain volumes in HIV-positive individuals, presumably due to atrophy, and individuals with older brain-predicted ages, relative to chronological age, showed deficits in a range of cognitive domains [8]. These findings suggest that chronic HIV disease may cause abnormal brain ageing, although it remains unclear whether ageing is accentuated or actually accelerated in this context.

Biological age can be assessed by a set of around ten biomarkers identified through the EU Framework Programme 7 “MARK-AGE” project. These variables, selected as best predictors of chronological age from among approximately 400 candidate biomarkers and combined using a set of weights, have been found to strongly predict biological age. In the COBRA study (Comorbidity in Relation to AIDS), investigators compared biological age with chronological age in older people with HIV and in a similar group of HIV-negative controls. They found that biological age was significantly greater than chronological age by 13.2 years (95% CI: 11.6, 14.9) in the HIV-positive group and by 5.5 (95% CI 3.8, 7.2) years in the HIV-negative group ($p < 0.001$ for each) with a significant difference between the two groups ($p < 0.001$) [9]. This underlines that what was shown in the blood in Down syndrome patients is mirrored in the brain in HIV subjects. Persons with an

elevated biological age also show signs in other domains such as evidence of cognitive decline. Indeed, Belsky et al. studied ageing in 954 young humans from the Dunedin Study birth cohort, tracking multiple biomarkers across three time points spanning their third and fourth decades of life [10]. They observed that young individuals of the same chronological age varied in their "biological ageing", showing declining integrity across multiple organ systems, and individuals who were ageing more rapidly were less physically able, showed cognitive decline and brain ageing, self-reported worse health and looked older [10].

Taken together, these data suggest that beyond a certain chronological age, it might be more useful to consider biological age to identify people who are at higher risk. Indeed, since ageing is the single most important risk factor for all major age-related diseases, a new discipline, termed geroscience, has emerged that seeks to understand how ageing enables chronic disease and develop novel multi-disease preventative and therapeutic approaches [11]. These authors purport that to combat age-associated diseases, the most effective strategy is likely to attempt to combat all of them together and not one by one. The trans-NIH Geroscience Interest Group summit described by the authors identified seven pillars underpinning not only the ageing process but also age-related diseases, namely, metabolism, macromolecular damage, epigenetics, inflammation, adaptation to stress, proteostasis and stem cells/regeneration [11]. Many human diseases that are or appear to be "clinically" different are conceptualized and treated separately, but they actually share basic molecular and cellular mechanisms, a phenomenon termed "diseasome" [12]. In an extension of this network theory of ageing, Franceschi et al. argued that a global reduction in the capacity to cope with a variety of stressors and a concomitant progressive increase in pro-inflammatory status are major characteristics of the ageing process, leading to a phenomenon they termed "inflammaging", brought on by a persistent state of antigenic load and stress [13]. Inflammaging is based on studies of the evolution of immune response and stress from invertebrates to mammals. The central cell in this phenomenon is the macrophage, playing the key role not only in the inflammatory response and immunity but also in stress response [13]. Damaged cells released into the body have a systemic effect on many other systems, propagating disease through the cells systemically through the body. Indeed, it is hypothesized that the basic stimuli for inflammation are cell debris [14]. Every day, in our body, thousands, not to say millions, of cells are destroyed and undergo necrosis or apoptosis, and the cell material becomes misplaced. Macrophages may interpret the displaced debris as an inflammatory stimulus, and the large amounts of mitochondrial DNA circulating confer considerable inflammatory power [14].

The other major players in this process are senescent cells and age-related changes in gut microbiota. A study of gut microbiota composition among young adults, elderly and centenarians observed that the microbial composition and diversity of the gut ecosystem of young adults and 70-year-old people were highly similar but differed significantly from that of the centenarians [15]. The findings suggested that core microbiota (most abundant bacterial species) decrease in frequency, but there is continuous remodelling, and subdominant species increase and rearrange their co-occurrence network [16]. This profound remodelling substantially changes

the profile in later life. Overall, there is evidence to suggest that time, geography and life experience can shape one's immune system in later ages [17]. It has been suggested that "trained immunity" can be induced after a primary infection or vaccination, conferring protection against a secondary infection through mechanisms that are independent of T/B cell adaptive responses [18], and this may be involved in the non-specific protective effect of vaccines. There are also data suggesting the influence of the microbiota on vaccine effectiveness [19], which could at least partially explain why some people respond while others do not. Half of the immune system is in our gut, and when there is microbial dysbiosis, systems do not function the same as when there is normal homeostasis. Diet may influence the immune status through the gut microbiota, therefore also influencing vaccine effectiveness. Many micronutrients are important for gut function, and it has been suggested to use probiotics and antibiotics to improve immune system effectiveness [20]. This could explain differences in vaccine efficacy between countries, for example.

Overall, there remain significant gaps in our knowledge regarding the effects of nutrition in vaccine efficacy, and complex biological, immunological, genetic, behavioural and environmental factors are intricately involved in the outcome of vaccination. There remain many exciting avenues of research to explore in all these areas to help identify to maximize the protection afforded by vaccines to people of all ages and backgrounds across the world.

References

1. Wiedermann U, Garner-Spitzer E, Wagner A. Primary vaccine failure to routine vaccines: why and what to do? Hum Vaccin Immunother. 2016;12(1):239–43.
2. Deelen J, Beekman M, Capri M, Franceschi C, Slagboom PE. Identifying the genomic determinants of aging and longevity in human population studies: progress and challenges. BioEssays. 2013;35(4):386–96.
3. Horvath S. DNA methylation age of human tissues and cell types. Genome Biol. 2013;14(10):R115.
4. Horvath S, Pirazzini C, Bacalini MG, Gentilini D, Di Blasio AM, Delledonne M, et al. Decreased epigenetic age of PBMCs from Italian semi-supercentenarians and their offspring. Aging (Albany NY). 2015;7(12):1159–70.
5. Horvath S, Garagnani P, Bacalini MG, Pirazzini C, Salvioli S, Gentilini D, et al. Accelerated epigenetic aging in down syndrome. Aging Cell. 2015;14(3):491–5.
6. Dall'Olio F, Vanhooren V, Chen CC, Slagboom PE, Wuhrer M, Franceschi C. N-glycomic biomarkers of biological aging and longevity: a link with inflammaging. Ageing Res Rev. 2013;12(2):685–98.
7. Borelli V, Vanhooren V, Lonardi E, Reiding KR, Capri M, Libert C, et al. Plasma N-glycome signature of down syndrome. J Proteome Res. 2015;14(10):4232–45.
8. Cole JH, Underwood J, Caan MW, De Francesco D, van Zoest RA, Leech R, et al. Increased brain-predicted aging in treated HIV disease. Neurology. 2017;88(14):1349–57.
9. De Francesco D, Oehlke S, Burkle A, Wit FW, Franceschi C, Kootstra NA, et al. Biomarkers of ageing in HIV-positive individuals and matched controls. Conference on Retroviruses and Opportunistic Infections; Seattle, Washington, February 13–16. Abstract P672. 2017. http://www.croiconference.org/sites/default/files/posters-2017/672_DeFrancesco.pdf. Accessed 18 Feb 2018.

10. Belsky DW, Caspi A, Houts R, Cohen HJ, Corcoran DL, Danese A, et al. Quantification of biological aging in young adults. Proc Natl Acad Sci U S A. 2015;112(30):E4104–10.
11. Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, et al. Geroscience: linking aging to chronic disease. Cell. 2014;159(4):709–13.
12. Barabasi AL. Network medicine—from obesity to the "diseasome". N Engl J Med. 2007;357(4):404–7.
13. Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000;908:244–54.
14. Franceschi C, Garagnani P, Vitale G, Capri M, Salvioli S. Inflammaging and 'Garb-aging'. Trends Endocrinol Metab. 2017;28(3):199–212.
15. Biagi E, Nylund L, Candela M, Ostan R, Bucci L, Pini E, et al. Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians. PLoS One. 2010;5(5):e10667.
16. Biagi E, Franceschi C, Rampelli S, Severgnini M, Ostan R, Turroni S, et al. Gut microbiota and extreme longevity. Curr Biol. 2016;26(11):1480–5.
17. Grignolio A, Mishto M, Faria AM, Garagnani P, Franceschi C, Tieri P. Towards a liquid self: how time, geography, and life experiences reshape the biological identity. Front Immunol. 2014;5:153.
18. Netea MG, Quintin J, van der Meer JW. Trained immunity: a memory for innate host defense. Cell Host Microbe. 2011;9(5):355–61.
19. Valdez Y, Brown EM, Finlay BB. Influence of the microbiota on vaccine effectiveness. Trends Immunol. 2014;35(11):526–37.
20. Praharaj I, John SM, Bandyopadhyay R, Kang G. Probiotics, antibiotics and the immune responses to vaccines. Philos Trans R Soc Lond Ser B Biol Sci. 2015;370(1671):20140144.

7 Profiling Vaccines for an Immunosenescent and Multimorbid Population

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Life expectancy is continuing to increase worldwide, and a recent report in *The Lancet* estimated that there is a 57% probability that life expectancy at birth among South Korean women in 2030 will be higher than 90 years and a 90% probability that it will be higher than 86.7 years [1]. Over the 3 million years of human evolution, and for 99.99% of the history of mankind, life expectancy was <30 years, but we have gained 55 years of life expectancy since 1700 and 35 years since 1900. So why has life expectancy increased so dramatically in recent years? In 1900, life expectancy in the United States was 47 years, compared to around 80 years now. This begs the question: What did people die of in 1900, and what do they die of today? At the beginning of the last century, infectious diseases were the cause of 57% of deaths. These diseases included diphtheria, tetanus, measles, smallpox, typhoid fever, pertussis and cholera. By 1998, the proportion of deaths due to infectious diseases had declined to <5%, and nowadays, non-communicable diseases such as ischemic heart disease, stroke, cancer, diabetes or Alzheimer's disease account for the majority of deaths. Evidently, life expectancy has been spectacularly increased by conquering infectious diseases through hygiene, clean water and vaccines. Vaccines have made an enormous contribution to controlling disease in infants and children, decreasing infant mortality and improving health among adults [2].

So one might wonder, what is next for vaccines? Have they reached the end of the road? The answer is a resounding no, as vaccines clearly still have a lot to contribute to society. The focus is now moving towards new target groups for vaccination, such as pregnant women or the elderly. These populations have not traditionally been the primary audience for vaccines, but are now garnering increasing attention as having the potential to yield considerable benefit from vaccination. Vaccines available for elderly include influenza (flu) and pneumococcal vaccines. Also, a

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_7

vaccine for herpes zoster is also now available, although efficacy declines with age, and uptake remains low. Up to now, the industry never developed vaccines specifically for elderly, but rather, recycled childhood vaccines for use among the elderly. However, this paradigm is now changing, and specific plans to develop vaccines for the elderly are afoot, bringing together vaccinologists and immunologists to tailor the technology of vaccine to the elderly population.

Vaccination first started to be investigated by Jenner and Pasteur in the late 1700s and 1800s, respectively, using the basic empirical technique of growing a disease-causing pathogen, then inactivating by attenuating or killing it, and then injecting it into a subject. However, in the last 30 years, new advanced technologies have made it possible to produce vaccines that were previously impossible. Recombinant DNA, glycoconjugation and reverse vaccinology are part of an explosion of new technologies in immunology and synthetic biology, opening broad new horizons in vaccine technology. Innovations such as reverse vaccinology have revolutionized how vaccines are conceived over the last two decades. Indeed, genome sequencing has made it possible to discover novel vaccine antigens derived directly from genomic information [3]. The first vaccine to be derived by this process, namely, a vaccine against meningococcus B, is now available on the market and is administered systematically to all newborns in the United Kingdom since September 2015. Over the first 10 months of its use, two-dose vaccine effectiveness was reported to be 82.9% (95% CI 24.1–95.2) [4]. This new era of designing vaccines has been ushered in by technological progress in such areas as human immunology, structural biology and genomics, by opening new avenues of research into protective human immune response. The advent of high-throughput DNA sequencing has made it possible to map entire bacterial genomes, bringing to light a range of previously unknown vaccine antigens [5]. Genomics is used not only for antigen discovery but also for antigen expression, for conservation and for epidemiology [3]. In addition, computational advances have enabled rapid identification of potential vaccine antigens from among the wealth of genetic and immunological information that can be obtained in shorter times than ever before [6]. Reverse vaccinology has made it possible to target many pathogens that were difficult or impossible before, including superbugs, and may help to pave the way towards vaccines for the most problematic infectious diseases such as tuberculosis, malaria, HIV or hepatitis C.

Next-generation technologies in vaccine development include structural vaccinology or structure-based antigen design. A recent study of the prefusion structure of respiratory syncytial virus (RSV) fusion (F) glycoprotein identified antibodies that bind prefusion-specific antigenic sites, including one antibody, 5C4, that was found to be 50-fold more potent than the only available licensed monoclonal antibody to treat RSV, namely, palivizumab [7]. This study provided important evidence that antibodies against the site of vulnerability on the prefusion RSV F conformation can be induced. These studies provided the basis of the structure-based design of new stable and powerful immunogens that are now used for the development of an effective vaccine against RSV. Further next-generation technologies include synthetic biology, which uses viral vectors (e.g. CMV, adenovirus alphavirus), and synthetic nucleic acids such as RNA and DNA to deliver the genome into the cell and

teach the organism how to generate their own the vaccine subunits. Eventually, we may achieve the production of fully synthetic vaccines.

To enhance our understanding of the immune system, and how these new vaccines may elicit protection, systems biology is changing the paradigm in clinical trials. The conventional approach of taking large numbers of people and recording a limited number of variables for each can be replaced by systems biology, a new approach where few subjects can deliver large volumes of data. Large-scale screening for unknown components and connections within the immune system, notably using recent—omics technologies, in conjunction with powerful computational capacity to identify patterns and develop models of behaviour, will allow us to target specific functions or diseases with greater precision [8].

It is well established that immunity wanes with increasing age, as a result of the progressive deterioration of innate and adaptive immune responses [9]. In an approach termed "systems vaccinology," high-dimensionality studies of cellular and molecular responses to vaccines have been proposed to help formulate hypotheses regarding the mechanisms of immunosenescence and to identify potential biomarkers worthy of investigation. There is a growing body of evidence indicating that vaccine response is a function of the "bio-age" of a person's immune system. Fourati et al. recently reported that bio-age is determined by transcriptomic changes, with upregulation of several pro-inflammatory pathways in the elderly, likely to favour immunosenescence [10]. Conversely, participants with a younger bio-age showed more transcriptional modules involved in B-cell signalling and T-cell receptors. Finally, the bio-age score developed by Fourati et al. was able to distinguish between two groups of elderly patients (≥65), namely, "BioAge young" (aged 65–78) and "BioAge old" (aged 65–83), and both the bio-age score and the two groups of elderly identified by the bio-age signature were significantly associated in response to hepatitis B vaccine [10]. These findings show, for the first time, that it may be possible to identify, prior to vaccination, participants likely to be poor vaccine responders.

Adjuvant technology is a major component of vaccine development and, until recently, was a field with a relatively slow pace of development. Adjuvant substances added to vaccines for their synergistic, immune-enhancing effects have been in use for almost a century. Aluminium salts were the first adjuvant substances to be used in human vaccines and, indeed, remained the only adjuvant used in licensed vaccines for around 70 years [11]. Since the late 1990s, there has been an acceleration in new adjuvants. The oil-in-water emulsion MF59 was a key innovation and the first novel adjuvant to be released for many years. The MF59 adjuvanted trivalent inactivated vaccine (ATIV) was shown in a randomized trial to be efficacious against PCR-confirmed influenza in infants and young children, increasing vaccine efficacy from 43% to 86% [12]. ATIV also showed a satisfactory safety profile, with no difference in serious adverse events between groups [12]. A prospective, observational study evaluating the relative effectiveness of ATIV versus non-adjuvanted trivalent inactivated vaccine (TIV) in elderly (65 years and older) subjects in Lombardy, Italy, reported that the risk of hospitalization for influenza or pneumonia was 25% lower with ATIV [13]. AS01, a

liposome-based vaccine adjuvant system, has been shown to enhance specific immune responses to the antigen for selected candidate vaccines targeting malaria and herpes zoster [14]. A phase 3 study of the efficacy, safety and immunogenicity of candidate malaria vaccine RTS,S/AS01 reported that the vaccine provided protection against both clinical and severe malaria in African children [15]. Regarding herpes zoster, a subunit vaccine containing varicella–zoster virus glycoprotein E and the AS01B adjuvant system was found to significantly reduce the risk of herpes zoster in adults aged 50 years or older in a randomized trial, with vaccine efficacy between 96.6% and 97.9% for all age groups [16]. These developments open new avenues in vaccine development, particularly indicating the potential to develop new vaccines specifically for elderly populations, as opposed to simply recycling children's vaccines for use among adults.

In conclusion, recent developments in vaccine technology, combined with next-generation technologies such as structural vaccinology, systems biology and systems vaccinology, have enabled significant progress in our knowledge of immune response and how it can be stimulated. The future may bring vaccines for illnesses previously considered impossible to prevent and in populations with immunosenescence.

References

1. Kontis V, Bennett JE, Mathers CD, Li G, Foreman K, Ezzati M. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. Lancet. 2017;389(10076):1323–35.
2. Rappuoli R, Mandl CW, Black S, De Gregorio E. Vaccines for the twenty-first century society. Nat Rev Immunol. 2011;11(12):865–72.
3. Rappuoli R, Bottomley MJ, D'Oro U, Finco O, De Gregorio E. Reverse vaccinology 2.0: human immunology instructs vaccine antigen design. J Exp Med. 2016;213(4):469–81.
4. Parikh SR, Andrews NJ, Beebeejaun K, Campbell H, Ribeiro S, Ward C, et al. Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study. Lancet. 2016;388(10061):2775–82.
5. Dormitzer PR, Grandi G, Rappuoli R. Structural vaccinology starts to deliver. Nat Rev Microbiol. 2012;10(12):807–13.
6. Liljeroos L, Malito E, Ferlenghi I, Bottomley MJ. Structural and computational biology in the design of immunogenic vaccine antigens. J Immunol Res. 2015;2015:156241.
7. McLellan JS, Chen M, Leung S, Graepel KW, Du X, Yang Y, et al. Structure of RSV fusion glycoprotein trimer bound to a prefusion-specific neutralizing antibody. Science. 2013;340(6136):1113–7.
8. Germain RN. Will systems biology deliver its promise and contribute to the development of new or improved vaccines? What really constitutes the study of "systems biology" and how might such an approach facilitate vaccine design. Cold Spring Harb Perspect Biol. 2017;10(8). https://doi.org/10.1101/cshperspect.a033308.
9. Goronzy JJ, Weyand CM. Understanding immunosenescence to improve responses to vaccines. Nat Immunol. 2013;14(5):428–36.
10. Fourati S, Cristescu R, Loboda A, Talla A, Filali A, Railkar R, et al. Pre-vaccination inflammation and B-cell signalling predict age-related hyporesponse to hepatitis B vaccination. Nat Commun. 2016;7:10369.

11. Di Pasquale A, Preiss S, Tavares Da Silva F, Garcon N. Vaccine adjuvants: from 1920 to 2015 and beyond. Vaccines (Basel). 2015;3(2):320–43.
12. Vesikari T, Knuf M, Wutzler P, Karvonen A, Kieninger-Baum D, Schmitt HJ, et al. Oil-in-water emulsion adjuvant with influenza vaccine in young children. N Engl J Med. 2011;365(15):1406–16.
13. Mannino S, Villa M, Apolone G, Weiss NS, Groth N, Aquino I, et al. Effectiveness of adjuvanted influenza vaccination in elderly subjects in northern Italy. Am J Epidemiol. 2012;176(6):527–33.
14. Didierlaurent AM, Laupeze B, Di Pasquale A, Hergli N, Collignon C, Garcon N. Adjuvant system AS01: helping to overcome the challenges of modern vaccines. Expert Rev Vaccines. 2017;16(1):55–63.
15. Rts SCTP, Agnandji ST, Lell B, Soulanoudjingar SS, Fernandes JF, Abossolo BP, et al. First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children. N Engl J Med. 2011;365(20):1863–75.
16. Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang SJ, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med. 2015;372(22):2087–96.

Comprehensive Geriatric Assessment in Infectious Diseases

8

Alberto Pilotto

Comprehensive geriatric assessment (CGA) is a multidimensional, interdisciplinary diagnostic process to determine the medical, psychological and functional capabilities of a frail elderly person in order to develop a coordinated and integrated plan for treatment and long-term follow-up [1, 2]. The clinical basis for the development of CGA was primarily the heterogeneity of the ageing population. Indeed, the ageing process manifests itself in a wide variety of ways, affecting a large spectrum of capacities and functions, due to the complex interplay of genetics, biology, disability, disease, cognitive status, psychosocial conditions, income, family, cohabitation, etc. In order to be able to perform an assessment, all these different variables need to be measured and integrated into a unique parameter, i.e. CGA.

From a clinical point of view, in addition to medical clinical evaluation, a range of other aspects need to be assessed, including functional and cognitive performance, and mood, using appropriate tools, in order to calculate the overall biological risk in terms of nutrition and then perform social evaluation, covering home life, social network, income and available resources. The ultimate objective is to characterize the clinical profile, the pathological risk and the residual skills, with a view to developing an individualized care plan.

CGA has demonstrated its efficacy in a range of settings, as shown in a recent review of three decades of trials from different healthcare settings and conditions [3]. In this review, it was shown that CGA was significantly useful in reducing such outcomes as mortality, functional decline, institutionalization or readmission, both in-hospital and long-term, and in different clinical settings including solid cancers, orthogeriatrics, preoperative assessment and patients with cognitive impairment [3]. Both home CGA programmes and CGA performed in-hospital were shown to be

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_8

consistently beneficial for several health outcomes and in specific clinical conditions with tailored programmes for frail older patients.

Frailty is a state of vulnerability to external stressor events resulting from a cumulative decline in various physiological systems over a lifetime [4]. It is the most problematic expression of population ageing and is a known risk factor for various negative outcomes. Indeed, frail patients who experience a stressor event may be more prone to falls, delirium or fluctuating disability, ultimately resulting in increased care needs and admission to hospital or long-term care. CGA has become the internationally established method to assess elderly people in clinical practice, because it is sensitive to the reliable detection of degrees of frailty. CGA is the gold standard to detect frailty and should be used more widely in this context.

In several infectious diseases, there are risk factors related to functional disability. One study of modifiable risk factors for pneumonia requiring hospitalization in community-dwelling older adults found that by attributable fraction analysis, 11.5% of cases of pneumonia could be attributed to incident mobility limitation [5]. In another study of 90 hospitalized older adults with severe *Clostridium difficile* infection, poor functional status assessed by Katz's activities of daily living (ADL) was found to be associated with severity of infection [6]. A clinical review of urinary tract infections in older women found that functional disability was a risk factor for recurrent symptomatic urinary tract infection [7]. Furthermore, geriatric syndromes are common in older HIV-infected adults, particularly pre-frailty, difficulty with instrumental activities of daily living (IADLs) and cognitive impairment [8], and clinical care of older HIV-infection adults should include geriatric principles. So clearly, there is a compelling need to incorporate CGA into the management approaches whenever older adults are concerned.

After three decades of use, CGA is facing new challenges. From a methodological point of view, informatics, robotics and self-assessment present new horizons to which CGA needs to adapt. There are also continuing challenges in terms of evaluation, with the need to compare different methods in terms of discrimination, generalizability, feasibility and clinimetric properties. In terms of its clinical use, CGA needs to move from risk assessment to outcome measures and also needs to be incremented with quality of life evaluation and patient preferences [9].

In this regard, a CGA-based prognostic tool for clinical decision-making has been developed, combining the eight different domains of standard CGA (namely, ADL, IADL, cognitive, nutrition, motility, comorbidity, polypharmacy, cohabitation status) into one single cumulative index called the multidimensional prognostic index (MPI). The MPI yields a score that is a continuous number ranging from 0 (indicating lowest risk) to 1 (highest risk) [10]. From clinical practice, with appropriate cutoffs, the MPI identifies three risk categories, namely, low, moderate and severe risk of short-term (1 month) and long-term (1 year) mortality. This index has been used over the last 10 years in many clinical situations. In a study of 134 hospitalized patients with community-acquired pneumonia (CAP), mean age 78.7 ± 8.8 years, the MPI was found to be a sensitivity measure of the multidimensional risk assessment that might be useful in identifying elderly patients with CAP at different risk of mortality who probably need a different intensity of clinical

interventions. Importantly, the accuracy of the MPI in terms of sensitivity and specificity is significantly higher than that of the pneumonia severity index, enabling the MPI to identify patients at higher risk that warrant more intensive interventions [11]. In another study of 49 consecutive patients aged over 65 years with CAP (mean age 86.6 ± 7 years), mean MPI score was measured at admission and discharge in combination with procalcitonin serum levels, and MPI at discharge was found to be a significant predictor of 1-month mortality [12]. The addition of procalcitonin levels significantly improved the accuracy of MPI at admission in predicting 1-month mortality [12]. Similar efficacy of the MPI for predicting short- and long-term mortality has been demonstrated in the context of acute gastrointestinal bleed [13], transient ischemic attack [14], chronic kidney disease [15], cancer [16], heart failure [17] and dementia [18]. The evaluation of tools to identify frailty showed that the MPI and modified MPI had the highest quality score, as critically appraised using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) [19]. Another review of frailty measurements in research and clinical practice showed that only three tools are actually based on the CGA, namely, the Frailty Index of Accumulated Deficits [21]; the Fatigue, Resistance, Ambulation, Illness, Loss of Weight (FRAIL) Index [22], which is a screening tool; and the MPI, which is the only one developed and validated in Europe [20].

In this context, an ongoing project called MPI-Age, in conjunction with the European Commission and the EUGMS, will use the MPI to improve cost-effectiveness of interventions in multimorbid frail older persons. To date, this project has investigated the relation between the use of various drugs including statins, anticoagulants and anti-dementia drugs and mortality in older adults.

Regarding statin use, the majority of randomized controlled trials do not include patients aged older than 80 years, and, therefore, it may be hard to know whether the benefits of these drugs observed in younger adults can also be yielded by their older counterparts. Beyond the age of 80, people are very heterogeneous, with varying life expectancy, and regardless of whether they are frail or not, the decision to treat is not evidence-based. In a retrospective observational cohort study of 1712 community-dwelling older subjects, ≥65 years with diabetes mellitus who underwent a CGA evaluation to establish accessibility to homecare services or nursing home admission showed that 3-year mortality increased with increasing MPI, but statin prescription declined with risk groups [23]. After adjustment for propensity score quintiles (for the propensity to be treated with statins), statin treatment was significantly associated with lower 3-year mortality, irrespective of MPI group [23]. Thus, statin treatment appears to be useful in older frail people with comorbidities, regardless of multidimensional impairment, although the frailest patients are those least likely to be treated with statins [23]. Similar results were reported in a cohort of 2597 older subjects with coronary artery disease (CAD) confirming that statin treatment was significantly associated with reduced 3-year mortality independently of age and multidimensional impairment, although the frailest were less likely to be treated with statins [24]. The results are somewhat different for anti-dementia drugs. In a retrospective analysis of 6818 community-dwelling older people who underwent a Standardized Multidimensional Assessment Schedule for

Adults and Aged Persons (SVaMA) in Italy, the same authors found that anti-dementia treatment was significantly associated with lower mortality only in subjects with low or moderate mortality risk as assessed by the CGA-based MPI-SVaMA, but not in the high mortality risk group [25]. This finding is interesting because MPI grade was previously found to be associated with a metabolic signature [26], whereby the concomitant elevation of markers of inflammation, associated with a simultaneous reduction in multiple metabolic and hormonal factors, predicts mortality in hospitalized elderly patients.

There is therefore compelling evidence to suggest that the MPI is now poised to become a key parameter in infectious diseases and vaccination discussions. Indeed, a special interest group on infectious disease and CGA was formed at the EUGMS meeting held in Lisbon in 2016 to initiate a cross-national, observational, non-interventional survey of older patients with infectious diseases to evaluate in a "real-world" population of older hospitalized patients at different mortality risks as assessed by the MPI, the prevalence of various infectious (including vaccine-preventable) diseases.

In conclusion, the ageing of the world population calls for an innovative perspective. To this end, clinicians need to consider the prognostic information obtained through well-validated, accurate and calibrated prognostic indices to identify those patients who may benefit from interventions given with the aim of increasing survival.

References

1. Rubenstein LZ, Josephson KR, Wieland GD, English PA, Sayre JA, Kane RL. Effectiveness of a geriatric evaluation unit. A randomized clinical trial. N Engl J Med. 1984;311(26):1664–70.
2. Rubenstein LZ, Rubenstein LV. Multidimensional geriatric assessment. In: Fillit H, Rockwood K, Woodhouse K, editors. Brocklehurst's textbook of geriatric medicine and gerontology. 7th ed. Philadelphia, PA: Saunders Elsevier; 2010. p. 211.
3. Pilotto A, Cella A, Pilotto A, Daragjati J, Veronese N, Musacchio C, et al. Three decades of comprehensive geriatric assessment: evidence coming from different healthcare settings and specific clinical conditions. J Am Med Dir Assoc. 2017;18(2):192 e1–e11.
4. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752–62.
5. Juthani-Mehta M, De Rekeneire N, Allore H, Chen S, O'Leary JR, Bauer DC, et al. Modifiable risk factors for pneumonia requiring hospitalization of community-dwelling older adults: the health, aging, and body composition study. J Am Geriatr Soc. 2013;61(7):1111–8.
6. Rao K, Micic D, Chenoweth E, Deng L, Galecki AT, Ring C, et al. Poor functional status as a risk factor for severe *Clostridium difficile* infection in hospitalized older adults. J Am Geriatr Soc. 2013;61(10):1738–42.
7. Mody L, Juthani-Mehta M. Urinary tract infections in older women: a clinical review. JAMA. 2014;311(8):844–54.
8. Greene M, Covinsky KE, Valcour V, Miao Y, Madamba J, Lampiris H, et al. Geriatric syndromes in older HIV-infected adults. J Acquir Immune Defic Syndr. 2015;69(2):161–7.
9. Pilotto A, Sancarlo D, Daragjati J, Panza F. Perspective: the challenge of clinical decision-making for drug treatment in older people. The role of multidimensional assessment and prognosis. Front Med (Lausanne). 2014;1:61.

10. Pilotto A, Ferrucci L, Franceschi M, D'Ambrosio LP, Scarcelli C, Cascavilla L, et al. Development and validation of a multidimensional prognostic index for one-year mortality from comprehensive geriatric assessment in hospitalized older patients. Rejuvenation Res. 2008;11(1):151–61.
11. Pilotto A, Addante F, Ferrucci L, Leandro G, D'Onofrio G, Corritore M, et al. The multidimensional prognostic index predicts short- and long-term mortality in hospitalized geriatric patients with pneumonia. J Gerontol A Biol Sci Med Sci. 2009;64(8):880–7.
12. Pilotto A, Dini S, Daragjati J, Miolo M, Mion MM, Fontana A, et al. Combined use of the multidimensional prognostic index (MPI) and procalcitonin serum levels in predicting 1-month mortality risk in older patients hospitalized with community-acquired pneumonia (CAP): a prospective study. Aging Clin Exp Res. 2018;30(2):193–7.
13. Pilotto A, Ferrucci L, Scarcelli C, Niro V, Di Mario F, Seripa D, et al. Usefulness of the comprehensive geriatric assessment in older patients with upper gastrointestinal bleeding: a two-year follow-up study. Dig Dis. 2007;25(2):124–8.
14. Sancarlo D, Pilotto A, Panza F, Copetti M, Longo MG, D'Ambrosio P, et al. A Multidimensional Prognostic index (MPI) based on a comprehensive geriatric assessment predicts short- and long-term all-cause mortality in older hospitalized patients with transient ischemic attack. J Neurol. 2012;259(4):670–8.
15. Pilotto A, Sancarlo D, Franceschi M, Aucella F, D'Ambrosio P, Scarcelli C, et al. A multidimensional approach to the geriatric patient with chronic kidney disease. J Nephrol. 2010;23(Suppl 15):S5–10.
16. Giantin V, Valentini E, Iasevoli M, Falci C, Siviero P, De Luca E, et al. Does the multidimensional prognostic index (MPI), based on a comprehensive geriatric assessment (CGA), predict mortality in cancer patients? Results of a prospective observational trial. J Geriatr Oncol. 2013;4(3):208–17.
17. Pilotto A, Addante F, Franceschi M, Leandro G, Rengo G, D'Ambrosio P, et al. Multidimensional prognostic index based on a comprehensive geriatric assessment predicts short-term mortality in older patients with heart failure. Circ Heart Fail. 2010;3(1):14–20.
18. Pilotto A, Sancarlo D, Panza F, Paris F, D'Onofrio G, Cascavilla L, et al. The multidimensional prognostic index (MPI), based on a comprehensive geriatric assessment predicts short- and long-term mortality in hospitalized older patients with dementia. J Alzheimers Dis. 2009;18(1):191–9.
19. Warnier RM, van Rossum E, van Velthuijsen E, Mulder WJ, Schols JM, Kempen GI. Validity, reliability and feasibility of tools to identify frail older patients in inpatient hospital care: a systematic review. J Nutr Health Aging. 2016;20(2):218–30.
20. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: a review. Eur J Intern Med. 2016;31:3–10.
21. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal. 2001;1:323–36.
22. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging. 2012;16(7):601–8.
23. Pilotto A, Panza F, Copetti M, Simonato M, Sancarlo D, Gallina P, et al. Statin treatment and mortality in community-dwelling frail older patients with diabetes mellitus: a retrospective observational study. PLoS One. 2015;10(6):e0130946.
24. Pilotto A, Gallina P, Panza F, Copetti M, Cella A, Cruz-Jentoft A, et al. Relation of statin use and mortality in community-dwelling frail older patients with coronary artery disease. Am J Cardiol. 2016;118(11):1624–30.
25. Pilotto A, Polidori MC, Veronese N, Panza F, Arboretti Giancristofaro R, Pilotto A, et al. Association of antidementia drugs and mortality in community-dwelling frail older patients with dementia: the role of mortality risk assessment. J Am Med Dir Assoc. 2018;19(2):162–8.
26. Fontana L, Addante F, Copetti M, Paroni G, Fontana A, Sancarlo D, et al. Identification of a metabolic signature for multidimensional impairment and mortality risk in hospitalized older patients. Aging Cell. 2013;12(3):459–66.

9 Aetiology of Respiratory Tract Infections in Adults in Europe: Current Knowledge and Knowledge Gaps

Ingo Beyer

Respiratory diseases represent the third most common cause of death in Europe, including both chronic lower respiratory diseases and pneumonia. Lower respiratory infections remain the most deadly communicable disease, causing 3.2 million deaths worldwide in 2012, with an overall mortality estimated to be 7.3% in the USA/Canada, 9.1% in Europe, and over 13% in Latin America [1]. In view of the current trends towards population ageing, it is expected that the burden of infections such as community-acquired pneumonia (CAP) will continue to increase in the coming years, with the vast majority of deaths occurring among those aged 65 years or more.

A wide range of host factors are implicated in the aetiology of respiratory tract infections, including anatomical and functional changes. Many of these come on with ageing, including decreased chest wall compliance, decreased strength of the respiratory muscles, and age-related changes in lung parenchyma. These changes can increase functional residual capacity, but unless diseased, the adult respiratory system is capable of maintaining adequate gas exchange over the full lifespan. Indeed, some subjects at age 70 have the same respiratory capacity as a 20-year-old, reflecting the "bio-age" concept, whereby the actual chronological age does not necessarily correspond to the physiological profile of the body or "bio-age." However, older people are much more heterogeneous than younger adults in terms of physiological factors affecting physical function. One important aspect in older people is dysphagia. Indeed, there are age-related changes in taste and smell. Normally, healthy adults can aspirate small amounts of oropharyngeal secretions during sleep, without it giving rise to repeated clinical infections as the burden of virulent bacteria in the swallowed material is generally low, and because of the presence of an active forceful coughing reflex, with active mucociliary transport and normal reflexes. However, in older adults with overt dysphagia, aspiration is

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_9

considered one of the most important mechanisms for lower respiratory infection. The prerequisites for aspiration pneumonia are dysphagia and aspiration (obvious or silent) and changes in oropharyngeal colonization or gastroesophageal reflux. Additionally, many older adults no longer have their own teeth, and it has been shown that 80% of dental prostheses become colonized, and using them at night may compound aspiration problems [2]. Particular attention to oral hygiene is necessary to ensure maximum protection against the risk of infection.

Age-related physiological changes, collectively designated by the term immune senescence, include factors such as the patient's lifetime history of antigen exposure, chronic or latent viruses, and adaptations to environmental stressors of the ageing host. All these factors combined may lead to chronic, low-grade inflammation (also known as "inflammaging"), resulting in an overall weakening of the subjects' immune status [3]. In line with these cellular changes, it is important to note, for example, that most of the influenza-specific B-cell responses in the elderly are based on mutational modifications of existing immune B cells rather than recruitment of naive B cells. All these anatomical and functional changes lead to an increased risk of pneumonia, often with an atypical presentation that renders diagnosis more difficult in this population [4, 5].

Beyond the physiological changes related to ageing, a second important question is: What are the pathogens responsible for lower respiratory tract infections (LRTI) in the elderly? While the pathogens and frequency observed in pneumonia in the very old are similar to younger patients, defining the aetiology of pneumonia is difficult [4]. Indeed, the microbiological diagnosis of pneumonia is different, and the yield of microbiological samples is so poor that the American guidelines do not even recommend microbiological sampling. European guidelines recommend blood cultures, sputum sample, and urinary antigen detection. In a study investigating the positivity rate, detection rates for non-covered pathogens, and the therapeutic impact of microbiological samples in community-acquired pneumonia (CAP), nursing home-acquired pneumonia (NHAP), and hospital-acquired pneumonia (HAP) in elderly hospitalized patients aged 75 years and over, Putot et al. showed that less than 20% of patients gave sputum samples and rates of samples were even lower in nursing-home acquired cases [6]. Blood cultures were easy to obtain, but less than 10% identified a pathogen. Therefore, samples yield low rates of positive pathogen identification. The important point to note is that in almost three quarters of patients, there is no documentation of the pathogen at all. Putot et al. concluded that microbiological samples, taken in over 90% of patients, did not yield any significant outcome-related benefits, and, therefore, they do not support systematic sampling in adults with LRTI [6]. They advise improving the efficiency of sampling by limiting these investigations to the period before initiation of antimicrobials and to those analyses, which would actually change the antibiotic treatment (such as not performing urinary antigen for streptococcal pneumonia when treatment active against that pathogen is already in place). However, it should be noted that bronchoalveolar lavage is well tolerated in older adults, and in non-responders, more invasive exams should be considered without hesitation. Putot et al. also suggest that more accurate tools are needed (such as molecular biology).

Coincidentally, Gadsby et al. published a study in 2016 using multiplex real-time PCR for 26 pathogens [7]. More than 80% of patients had already received antibiotics by the time the sample was obtained, and this is usually considered a barrier to identification of the pathogen. Nonetheless, the authors reported pathogen detection in 87% with CAP, compared with 39% using culture-based methods. Viruses were present in 30% of patients, which is more than previously indicated. Viruses alone were found in only 5.6% of cases, and when a virus was detected, 81.6% were codetected with bacteria. 31.6% had multiple bacterial pathogens, and agreement between PCR-positive and culture-positive results was 98.4%. Among the 85% of patients who received antibiotics in the 72 h before admission, 78% had a bacterial pathogen detected by PCR, but only 32% were culture positive. It is particularly noteworthy that many pathogens colonize the oropharyngeal cavity, and with PCR, there may be a risk of overdiagnosis. Therefore, the authors standardized the curve to see if the PCR results showed sufficient material load to conclude it was infection and not just colonization (cut-off, >100,000 colony-forming units). The most important finding of this study was that over 75% of patients could have benefitted from de-escalation of therapy from broad-spectrum empirical antimicrobials to pathogen-directed therapy, and this is of paramount importance for antibiotic resistance.

What is the effect of vaccination on microbiology? In the USA, due to wide vaccination programmes, the contribution of streptococcus to pneumonia has decreased, accompanied, however, by increased resistance of remaining streptococcal strains to several antibiotics since the introduction of the pneumococcal conjugate vaccine (PCV) [8]. This was recently addressed in a Swiss report that examined invasive and noninvasive pneumococcal isolates, showing that noninvasive isolates came primarily from children (those who are vaccinated) and that resistance was quite low, and was even found to be slightly decreasing in adults, suggesting that antibiotic resistance does not increase after vaccination [9]. Furthermore, immunization in children is an important tool for preventing infection in adults (herd protection). Concerning vaccination in older adults, PPV23 has not been shown to be able to reduce pneumonia, and PCV13 reduces vaccine-type pneumococcal pneumonia but does not reduce CAP from any cause [10–12]. In addition, there appears to be lesser vaccine efficacy of the influenza vaccine in older adults. Several papers, however, suggest that the association of both vaccines has additive effects and could reduce the risk of pneumonia and mortality by about 25% [13–16].

The following knowledge gaps remain in the oldest old (>85 years of age): most samples come from hospitalized patients, and few data are available in patients treated at home or in nursing homes. In addition, the microbiology in patients who cannot provide sputum remains unknown. However, documenting pathogens is only useful if it actually changes patient outcomes. It remains to be seen whether prospective studies can prove that molecular biology-guided de-escalation in antibiotic therapy would reduce resistance, reduce antibiotic use, and improve patient outcomes.

In conclusion, molecular techniques should be used for timely identification of pathogens in LRTI, and this technology remains useful and informative even in patients who are already receiving antibiotics. We need to be mindful of increasing

antibiotic resistance, hence the utility of pathogen identification to allow pathogen-specific treatment. Despite insights in microbiology, mortality remains high, underscoring the importance of preventive vaccination strategies. An additive effect of dual PCV/flu vaccination has been described. Host factors play a major role in LRTI in older adults and should always be addressed, e.g. detection of silent aspirations, screening of medication to decrease dry mouth and swallowing problems, and emphasis on the importance of denture and oral hygiene. Sarcopenia should also be addressed in older adults to reduce risk of LRTI, and physicians should beware of the often atypical disease presentation in this population.

References

1. World Health Organisation. The top 10 causes of death. 2017. http://www.who.int/mediacentre/factsheets/fs310/en/. Accessed 7 Aug 2017.
2. Vanden Abbeele A, de Meel H, Ahariz M, et al. Denture contamination by yeasts in the elderly. Gerodontology. 2008;25:222–8.
3. Goronzy JJ, Weyand CM. Understanding immunosenescence to improve responses to vaccines. Nat Immunol. 2013;14:428–36.
4. Janssens JP, Krause KH. Pneumonia in the very old. Lancet Infect Dis. 2004;4:112–24.
5. Faverio P, Aliberti S, Bellelli G, et al. The management of community-acquired pneumonia in the elderly. Eur J Intern Med. 2014;25:312–9.
6. Putot A, Tetu J, Perrin S, et al. Impact of microbiological samples in the hospital management of community-acquired, nursing home-acquired and hospital-acquired pneumonia in older patients. Eur J Clin Microbiol Infect Dis. 2016;35:489–95.
7. Gadsby NJ, Russell CD, McHugh MP, et al. Comprehensive molecular testing for respiratory pathogens in community-acquired pneumonia. Clin Infect Dis. 2016;62:817–23.
8. Jones RN, Sader HS, Moet GJ, et al. Declining antimicrobial susceptibility of Streptococcus pneumoniae in the United States: report from the SENTRY antimicrobial surveillance program (1998–2009). Diagn Microbiol Infect Dis. 2010;68:334–6.
9. Hauser C, Kronenberg A, Allemann A, et al. (2016) Serotype/serogroup-specific antibiotic non-susceptibility of invasive and non-invasive streptococcus pneumoniae, Switzerland, 2004–2014. Euro Surveill. 21(21). https://doi.org/10.2807/1560-7917.ES.2016.21.21.30239.
10. Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015;372:1114–25.
11. Diao WQ, Shen N, Yu PX, et al. Efficacy of 23-valent pneumococcal polysaccharide vaccine in preventing community-acquired pneumonia among immunocompetent adults: a systematic review and meta-analysis of randomized trials. Vaccine. 2016;34:1496–503.
12. Kraicer-Melamed H, O'Donnell S, Quach C. The effectiveness of pneumococcal polysaccharide vaccine 23 (PPV23) in the general population of 50 years of age and older: a systematic review and meta-analysis. Vaccine. 2016;34:1540–50.
13. Christenson B, Hedlund J, Lundbergh P, et al. Additive preventive effect of influenza and pneumococcal vaccines in elderly persons. Eur Respir J. 2004;23:363–8.
14. Christenson B, Pauksen K, Sylvan SP. Effect of influenza and pneumococcal vaccines in elderly persons in years of low influenza activity. Virol J. 2008;5:52.
15. Mahamat A, Daures JP, de Wzieres B. Additive preventive effect of influenza and pneumococcal vaccines in the elderly: results of a large cohort study. Hum Vaccin Immunother. 2013;9:128–35.
16. Zhang YY, Tang XF, Du CH, et al. Comparison of dual influenza and pneumococcal polysaccharide vaccination with influenza vaccination alone for preventing pneumonia and reducing mortality among the elderly: a meta-analysis. Hum Vaccin Immunother. 2016;12:3056–64.

10 European Flu Vaccine Regulations and Their Impacts in Community-Dwelling Adults

Jacques Gaillat

There are two sides to vaccine regulations. The first side concerns vaccine registration and comprises guidelines for vaccines manufacturers covering the quality, regulatory, nonclinical and clinical aspects of the development of influenza vaccines. The guidelines also stipulate the requirements for obtaining marketing authorisation for all influenza vaccines and outline clinical immunogenicity and vaccine effectiveness aspects as well as post-authorisation pharmacovigilance requirements. Furthermore, the European Medicines Agency (EMA) issues an annual update with recommendations for the strains that vaccine manufacturers should include in the seasonal flu vaccine following the WHO's recommendations.

The other side concerns recommendations for the vaccines, i.e. those who need to be vaccinated. The European Council issued a recommendation on 22 December 2009 on seasonal influenza vaccination, and in this statement, the Council recognizes the burden of disease in at-risk populations [1]. Concerted action is undertaken to increase flu vaccine coverage (notably by setting target levels in various groups). A strategy against a flu pandemic is also recognized as being of prime public health importance. Healthcare workers (HCW) should be made aware of the danger faced by their more vulnerable patients, and the need to gather specific and comparable data at national level is underlined. Indeed, a good tool to achieve this goal is the European Centre for Disease Control, to provide technical and scientific expertise to the European Community and member states. In light of the points recognized in relation to flu vaccination, the Council encourages member states to adopt and implement national, regional or local action plans or policies to reach target vaccination levels. There is clearly a need to improve coverage among HCW. Member states are further encouraged to measure uptake, and analyse the reasons why some people do not wish to receive vaccinations, as well as to foster education, and report outcomes of implementation of the recommendations.

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_10

Although these recommendations are enshrined in European Union law and theoretically applicable to all EU states, practices are highly variable across the EU nations. A technical report from the European Centre for Disease Control (ECDC), which is entrusted with the mission to provide technical and scientific expertise to the Commission and the member states, stated that only three countries have a national action plan for vaccination [2]. The report further stated that in 20 countries, there is no national action plan, although vaccination strategies are in place. Among 30 countries, all have different definitions of who should be vaccinated for influenza, for example—the threshold for "old" differs widely; and although all 30 countries agree that immunodepressed subjects should be vaccinated, again, definitions of these differ. Most countries agree that those with comorbid conditions constitute a group at risk and should be vaccinated. Yet, uptake ranges from above or at target levels in Scotland to below 10% in Romania, Latvia and Estonia. Only 10 countries responded regarding rates of uptake among older populations with chronic medical conditions, and most were below target levels.

Despite the details given in the ECDC report, it remains difficult to compare uptake between countries, because the figures are not calculated in the same way. In addition, the reasons why some people are reluctant to get vaccinated were not explored. Overall, despite the existence of pan-European recommendations, national action plans are at the discretion of the individual member states. There is relative consensus regarding who the target groups are, namely, older adults (although the threshold for defining "old" varies widely), HCW, immunosuppressed patients and pregnant women. Nonetheless, there remains large variation in vaccination practices and coverage rates across the EU.

A comparison of national plans or policymaking throughout the EU and their impact on vaccination coverage rates reveals that policymaking bodies, such as governments, professional societies, healthcare systems and national immunization technical advisory groups (NITAGS), all have different roles and interests in this process. NITAGs are a technical resource whose role is to propose a national immunization policy based on a measure of the public health burden and evaluation of the benefit to be gained from large-scale immunization in a specified population. They are responsible for knowledge synthesis and translating knowledge into recommendations. Yet, again, differences exist between NITAGs. Most agree to recommend universal routine use in target populations and individual vaccination based on the medical judgement of the healthcare provider.

Regarding funding for vaccination, almost all EU countries have national health service funding, albeit some with a small amount of out-of-pocket expense for the patient. Overall, there appears to be no clear relationship between funding and uptake.

Policy implementation may influence vaccine uptake. Blank et al. assessed the elements of vaccination policies and the influence of policy-related driving factors on vaccine coverage rates among the elderly [3]. In their report, 16 European National Vaccine Industry Groups (NVIGs) were included in a survey to make an inventory of vaccination policies implemented at national level in 2009, focussing on four topics, namely, management of vaccination programmes, influence of

HCWs, the role of information/communication campaigns and access to vaccines. The authors report that vaccination policies are implemented as a set, and not as stand-alone elements. They identified two key steps, namely, the need to monitor vaccine uptake rates and sending personal letters for free vaccines, which may be very useful. Another key player in the implementation of vaccine policies is the general practitioner (GP). In a European expert synthesis, Kassianos et al. provide practical guidance for GPs for the implementation of a seasonal influenza vaccination programme. To take full advantage of their potential as players in this domain, the GP must know about the guidelines, provide advice and answer patient's questions, send notification and material and organize and implement vaccination. Medical practices should have one person responsible for vaccination, and maintain a register of eligible individuals and monitor their status. The question of incentives for this service has been raised, although a critical review of the influence of welfare systems on pay-for-performance programmes for GPs shows that the evidence concerning the effectiveness of pay-for-performance systems is mixed, at best [4].

In terms of national initiatives, England has an annual flu plan, which is a tripartite holistic prevention and control plan, under the auspices of the Department of Health, the National Health System-England and Public Health England. It covers policy decisions relating to the flu season, oversight of the supply of antiviral medicines, procurement and distribution of vaccines, oversight of vaccine supply and strategic reserves and delivery of the vaccination programmes. It also follows through with monitoring and reporting of key indicators related to the flu, such as flu activity, vaccine uptake and vaccine effectiveness. It also includes a respiratory hygiene campaign. In this setting, the role of the GP is of paramount importance in England [5]. Indeed, the Health and Social Care Act of 2012 made GP practices and other providers responsible for ensuring that everyone who is eligible is invited personally to have their flu vaccine. GPs (and other providers) are also responsible for encouraging their own staff to be vaccinated and for putting the procedures in place to achieve this. NHS England commission GPs and community pharmacies to deliver the flu vaccination programme locally. Clearly, this is a face-to-face process that is fundamentally personal and therefore best delivered by local providers that the patient knows and trusts. These providers therefore have a proactive role in a dynamic process with adaptations possible from year to year based on feedback. A range of measures are put in place every year to ensure a successful campaign, including letters from the Chief Medical Officer to healthcare providers, an annual flu plan and annual updates of the Green Book (an NHS document containing the latest information on vaccines and vaccination procedures, for vaccine preventable infectious diseases in the UK). In addition, publicity campaigns for the public and health professionals are organized, aiming to achieve immunization targets of >75% for patients over 65 years of age and among healthcare workers, for example. Finally, the NHS also sends letters to GPs recommending that they prescribe antivirals, once the surveillance system has identified the circulating flu strains. Overall, it is hoped that flu vaccination uptake will rise.

France presents an interesting example of the challenges of achieving adequate vaccine coverage. Several years ago, France introduced free vaccines for older

subjects and those at risk. They receive a voucher by post to get the vaccine for free, the aim being to restore confidence in vaccination. However, it would appear that some simplification of the process is desirable as regards the flu vaccine. Indeed, for the 2008–2009 flu campaign, 66% of all those at-risk received the voucher and 68% in 2014–2015. Among those aged over 65, 93% and 91% received the voucher, respectively, in 2008–2009 and 2014–2015, although only around 40% of those aged under 65 and at risk received the voucher. Yet, there seems to be a clear decrease in vaccine uptake in France among the 65–69 age group, raising the question of what other factors are at play in this phenomenon. Indeed, there has been no decrease in funding, the rate of voucher distribution is practically identical, and there have been no change in GP or nurse vaccination participation and no change in national vaccine policy. In fact, the likely explanation for these observations is that France is a world leader in vaccine scepticism. The past pandemic campaign had a negative impact on public opinion, and this is reflected in an increase in vaccine hesitancy, with many remaining unconvinced of the utility and safety of vaccines. In a large-scale, data-driven survey on worldwide attitudes to immunization, Larson et al. examined perceptions of vaccine importance, safety, effectiveness and compatibility with religious beliefs among 65,819 individuals across 67 countries. They noted that vaccine-safety related sentiment is particularly negative in the European region, which accounts for 7 of the 10 least vaccine-confident countries. France ranked among these, with 41% of respondents reporting that they disagree that vaccines are safe, compared to a global average of 13%. Interestingly, countries with high levels of education and good health services were associated in this survey with lower rates of positive sentiment, suggesting an emerging inverse relationship between vaccine sentiment and socio-economic status [6].

Since 2007, the European Centre for Disease Prevention and Control (ECDC) has supported I-MOVE (influenza monitoring vaccine effectiveness), a network to monitor seasonal and pandemic influenza vaccine effectiveness in Europe. Since its inception, the I-MOVE teams have conducted multicentre case-control, cohort and screening method studies, undertaken within existing sentinel influenza surveillance systems [7]. Early estimates from a test-negative case-control study based on five European sentinel surveillance networks indicated that in early 2012/2013, adjusted influenza vaccine effectiveness was 50.4% (95% CI: −20.7–79.6) against all influenza types in the target groups for vaccination [8]. Results indicate that feedback on effectiveness must come in as fast as possible.

In conclusion, 8 years after the EU council, objectives in terms of immunization are still not met, with low vaccine coverage rates persisting. Despite the existence of national plans and structures to improve vaccine coverage rates, the heterogeneity of healthcare systems across Europe and the different histories of the individual countries render this a complex problem. Clearly, a "one-size-fits-all" approach is unsuitable, and a more holistic vision is needed. The EU magazine, *The Parliament Magazine*, has called for its members to take action on vaccine hesitancy and boost public confidence, with a more recent paper in the same magazine arguing that the success of vaccination programmes is based on citizens' trust in the safety of vaccines. Therefore, politicians are aware of the problem, and several papers have

addressed the issue, with plans and ideas for how to act towards better vaccine coverage [9–11]. It is a lifelong and intergenerational approach, and a cyclic, not a longitudinal vision.

References

1. Council of the European Union. Official Journal of the European Union. Council Recommendation of 22 December 2009 on season influenza vaccination (2009/1019/EU) Brussels; 2009.
2. European Centre for Disease Prevention and Control. Season influenza vaccination and antiviral use in Europe – overview of vaccination recommendations and coverage rates in the EU Member States for the 2013–14 and 2014–15 influenza seasons Stockholm ECDC; 2016.
3. Blank P, Schwenkglenks M, Szucs TD. The impact of European vaccination policies on seasonal influenza vaccination coverage rates in the elderly. Hum Vaccin Immunother. 2012;8:328–35.
4. Ammi M, Fortier G. The influence of welfare systems on pay-for-performance programs for general practitioners: a critical review. Soc Sci Med. 2017;178:157–66.
5. Pebody R. High-level hearing on the implementation of the Council Recommendation on seasonal influenza vaccination: implementation of seasonal influenza vaccination programme in the United Kingdom (UK). Respiratory Diseases Department, Public Health England, Luxembourg. 2015. April 2015.
6. Larson HJ, de Figueiredo A, Xiahong Z, et al. The state of vaccine confidence 2016: global insights through a 67-country survey. EBioMedicine. 2016;12:295–301.
7. Valenciano M, Ciancio B. I-MOVE: a European network to measure the effectiveness of influenza vaccines. Euro Surveill. 2012;17(39)
8. Kissling E, Valenciano M. Early estimates of seasonal influenza vaccine effectiveness in Europe among target groups for vaccination: results from the I-MOVE multicentre case-control study, 2011/12. Euro Surveill. 2012;17(15)
9. Gellin BG, Shen AK, Fish R, et al. The national adult immunization plan: strengthening adult immunization through coordinated action. Am J Prev Med. 2016;51:1079–83.
10. Mackay C. Call for EU member states to take action on ‘vaccine hesitancy’. The Parliament Magazine. 2015. 28 August 2015.
11. McMenamin J. Success of vaccination programmes is based on citizens’ trust in safety of vaccines. The Parliament Magazine. 2017. 2 May 2017.

Vaccination Against Pneumococcal Disease in the European Union, with Particular Focus on Germany

11

Gerhard Falkenhorst and Johan Flamaing

11.1 Background

Infection with *Streptococcus pneumoniae* (aka pneumococcus) may cause different clinical presentations. Usually, a distinction is made between invasive and noninvasive disease. Invasive pneumococcal disease (IPD) is defined by the detection of *S. pneumoniae* in a normally sterile body fluid, such as blood, pleural fluid or cerebrospinal fluid. The most common clinical picture in the elderly is pneumonia, but more severe types of disease like meningitis or septicaemia do occur. In children, less severe presentations like acute otitis media and sinusitis are common. *S. pneumoniae* is the most frequent pathogen found in community-acquired pneumonia (CAP) [1]. People with a weak immune system are at highest risk, such as children in the first years of life, older adults and immunocompromised patients of any age. Pneumococcal disease may be aggravated by pre-existing comorbidities (e.g. chronic heart, lung, kidney and liver disease). Incidence and mortality are highest in young children and older adults. To date, almost 100 different capsular serotypes of *S. pneumoniae* have been identified.

11.2 Vaccination Recommendations

Vaccines against *S. pneumoniae* have been available for many years. The 23-valent pneumococcal polysaccharide vaccine (PPSV23) was licenced in 1983. Because the immature immune system of infants responds poorly to pure polysaccharide

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_11

antigens, conjugated polysaccharide vaccines were developed for this age group. A 7-valent pneumococcal conjugate vaccine (PCV7), including the then most common serotypes, was licenced in 2000, followed by PCV10 and PCV13 in 2009. Initially, the conjugate vaccines were indicated for children <5 years only, but more recently (around 2010–2011 depending on the country), the indication of PCV13 was extended to adults.

The World Health Organization (WHO) states that vaccination of all infants with PCV is a priority and should be introduced in all countries [2]. However, in the same position paper, they also state that further data are needed on the impact of wide-scale PCV13 vaccination in adults (>50 years of age). The report goes on to say that evidence does not support routine immunization of the elderly and high-risk populations with PPV23. On the other hand, professional societies, such as the Escmid Vaccine Study Group (EVASG), European Geriatric Medicine Society (EUGMS) and the World Association for Infectious Diseases and Immunological Disorders (WAidid), recently issued guidelines for adult immunization [3], recommending sequential vaccination with PCV13 and PPSV23, thus combining the advantages of PCV13 (stronger immune response and induction of immune memory) with the broader serotype coverage of PPSV23. Such a strategy is recommended in the USA and some EU countries, while other EU countries and Canada recommend PPSV23 only or no routine vaccination of healthy older adults at all [4–6].

The Joint Committee on Vaccination and Immunisation (JCVI) in the United Kingdom (UK) recommended in their statement dating from late 2015 that PPSV23 should continue to be offered to those aged 65 years and over and the indicated risk groups, while PCV13 should be offered to those risk groups previously identified as being at particularly high risk of, and high mortality from, IPD, but should not be offered more widely to other risk groups or older adults [7]. These different viewpoints may leave many clinicians confused with regard to vaccination of their elderly patients.

11.3 Efficacy of Pneumococcal Polysaccharide Vaccines

The controversy goes even further. A Cochrane meta-analysis published in 2013 reviewed data from 18 randomized controlled trials (RCTs) involving 64,852 participants plus 7 non-RCTs involving 62,294 participants to assess PPSV efficacy/effectiveness. They found strong evidence of PPSV efficacy against IPD in adults, but the authors report that the evidence is less clear for adults with comorbidities, and an effect on all-cause pneumonia or mortality could not be demonstrated [8]. Yet, a more recent Cochrane meta-analysis examining the efficacy of pneumococcal vaccines in patients with chronic obstructive pulmonary disease (COPD) found that PPSV23 reduced the likelihood of community-acquired pneumonia and of COPD exacerbation by about 40%. The efficacy of PCV in this target group could not be assessed, because no relevant RCTs were identified [9].

An up-to-date meta-analysis of PPSV23 efficacy and effectiveness has been published in 2017 by author GF of this chapter and colleagues. We performed a

systematic literature review and meta-analysis of the vaccine efficacy/effectiveness (VE) of PPV23 against IPD and pneumococcal pneumonia in adults aged ≥60 years living in industrialized countries [10]. Across 17 eligible studies included in the analysis, we found significant VE of PPV23 against both IPD and pneumococcal pneumonia. Pooled VE against IPD (by any serotype) was 73% (95% CI: 10–92%) in four clinical trials, 45% (95% CI: 15–65%) in three cohort studies and 59% (95% CI: 35–74%) in three case-control studies.

Pooled VE against pneumococcal pneumonia was not significant when including all four clinical trials (VE = 25% (95% CI: −62 to 65%)), but heterogeneity among studies was high for this particular outcome (I^2 = 78%). This can be explained by two studies [11, 12] that used an unusual method of diagnosis, namely, detection of serum antibodies against pneumolysin, a cytotoxin produced by *S. pneumoniae*. Serum specimens from both studies were analysed in the same laboratory using a poorly validated in-house ELISA, which later has been shown to have a low specificity, thus biasing observed VE towards no effect [13, 14]. This assay has never been used in other published reports nor has it become part of routine practice. Sensitivity analysis excluding these two studies with a high risk of bias resulted in a significant efficacy of PPSV23 against pneumococcal pneumonia of 64% (95% CI: 35–80%). However, this result was mainly driven by one randomized trial [15], because the second trial remaining in the analysis [16] had a much smaller sample size.

To bolster these results, we included evidence from observational studies. The pooled vaccine effectiveness against pneumococcal pneumonia (by any serotype) in two cohort studies was 48% (95% CI: 25–63%) [10]. In summary, the current state of evidence is in favour of a significant protective effect of PPSV23 against IPD and pneumococcal pneumonia in the elderly.

11.4 Should Vaccination with PPSV23 Be Repeated?

Observed PPSV23 efficacy was higher in randomized clinical trials (with follow-up of 2.5 years) than in observational studies (follow-up 5 years), which may indicate that protection wanes over time. As revaccination is already recommended for people with specific risk conditions, including asplenia or chronic renal failure, it appears logical to recommend revaccination for those with age as a risk factor, too. A systematic literature review by Remschmidt et al. assessed the effectiveness and safety of repeated vaccination with PPSV23 [17]. Overall, they identified 14 observational studies, none of which reported effectiveness against clinical endpoints. Immunogenicity data showed that lower peak antibody levels were reached shortly after the second dose of PPSV23, but there were no salient differences in antibody levels thereafter. Compared to primary vaccination, revaccination appeared to be associated with a higher risk of side effects, but these were usually mild and resolved after 2–3 days, as also previously reported by Jackson et al., who concluded that this risk does not represent a contraindication to revaccination with PPSV23 for recommended groups [18].

11.5 Efficacy of Pneumococcal Conjugate Vaccines in the Elderly

The efficacy of PCV13 was investigated in a randomized, double-blind, placebo-controlled trial involving ~85,000 immunocompetent adults 65 years of age or older in the Netherlands (CAPITA trial [19]). Efficacy of PCV13 was 75.8% (95% CI: 46.5–90.3%) against IPD by serotypes included in PCV13 (vaccine types, VT) and 41.1% (12.7–60.7%) against non-bacteraemic and noninvasive pneumococcal CAP caused by VT. Regarding disease by any pneumococcal serotype, efficacy of PCV13 was 48.5% (20.9–67.0%) against IPD, but not significant against non-bacteraemic and noninvasive pneumococcal CAP (VE = 17.4% (−10.2 to 38.2%)).

All efficacy figures are those of the so-called modified intention-to-treat analysis. Efficacies in the "per-protocol analysis" were somewhat higher, but this analysis excluded subjects who had been immunocompetent at the time of vaccination but were immunodeficient when diagnosed with IPD or pneumonia [19]. Vaccine efficacy persisted over time (median follow-up of almost 4 years). However, it should be noted that people with immunodeficiency and people residing in nursing homes were excluded from the CAPITA trial, and only a minority of participants was older than 75 years (75–84 years, 27.8%; ≥85 years, 3.5%). A post hoc analysis of the CAPITA trial reported that the efficacy of PCV13 as predicted by the model for preventing vaccine-type specific CAP and IPD declined from 65% to 40% for subjects who were aged 65 and 75 years old, respectively, at the time of vaccination [20]. Therefore, the question about the efficacy of PCV13 in the oldest old remains open.

Efficacy against any CAP, regardless of pathogen, was reported as 5.1% (−5.1 to 14.2%). This reflects the fact that *S. pneumoniae* was identified as the causative agent in only 22% of the study participants diagnosed with pneumonia. This proportion is in line with data from other studies, mostly reporting percentages in the range of 20–30% [21].

11.6 Population Impact of Pneumococcal Vaccination Programmes

Vaccine coverage varies considerably across countries in the European Union. For example, in the UK, in 2016, 80% of those aged over 75 years were vaccinated, compared to less than 15% of the same age group in Belgium [22, 23]. In the face of poor coverage, an important question is whether there is herd protection of the elderly from infant vaccination with PCV. The USA has the longest history of pneumococcal vaccination in both adults and children, with good registration and surveillance systems in place, thus generating a large body of trustworthy data. The incidence of IPD in children declined hugely between 1998 and 2015, following the successive introduction of PCV7 and PCV13. A similar drop in incidence was also observed in adults aged 65 and over, indicating herd protection. This protection is also mirrored by mortality, with a considerable decline in mortality in children

between 1998 and 2015, but also in older adults, with mortality per 100,000 dropping from 4.02 to 0.24 in infants aged <1 year between 1998 and 2015 and from 11.02 to 6.12 in those aged over 65 years. Similarly, data from the national IPD registration system in England and Wales show that there was a decline in the number of IPD both in children under 2 and in older adults (>65 years) after the introduction of the PCV7 vaccine, followed by a further drop in both age groups after the introduction of PCV13. Separate analysis of the six additional serotypes included in PCV13 but not in PCV7 showed that the cumulative incidence of IPD caused by these serotypes also declined. This is further evidence in favour of a herd protection effect. However, the incidence of IPD due to non-vaccine serotypes increased. This so-called serotype replacement indicates that previously infrequent serotypes occupy the ecological niche formed by the removal of the serotypes included in PCV13. Although this represents a potential drawback to vaccination, there is nonetheless an overall reduction of disease burden through pneumococcal vaccination.

In terms of the epidemiology of pneumococcal disease in Europe, it is important to underline that differences in the quality of surveillance and in policies make implementation of uniform strategies for pneumococcal vaccination a demanding and puzzling task. Evidence is sparse in older adults and high-risk groups, and this is worth considering when reflecting on potential policy changes, as these are the groups at highest risk where the benefit is most likely the greatest. The direct and indirect (herd effect) impact of vaccinating children with PCV is high, and it remains difficult to distinguish between direct and indirect effects on PD when vaccinating older individuals. Lastly, surveillance of IPD incidence and case fatality is of paramount importance to monitor epidemiology. In this regard, there is a compelling need for uniform registration in all EU countries using systems with reliable and comparable indicators.

In addition, a lifelong vaccination policy is important from children through high-risk groups to older age. The European Centre for Disease Control and Prevention (ECDC) provides an overview of pneumococcal vaccine recommendations in the European Union (EU) member states [24]. It shows the wide variation in terms of vaccines recommended, age, reimbursement and populations considered. A uniform EU policy would promote harmonization of vaccination practices in member states. However, differences of the epidemiological situation and of the standards of healthcare provision among member states may justify diverging vaccination recommendations.

11.7 Vaccination Strategy Against Pneumococcal Disease: The Example of Germany

Since 1998, Germany's Standing Committee on Vaccination (Ständige Impfkommission, STIKO) has recommended vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) for all people aged ≥60 years. Universal vaccination of infants with a pneumococcal conjugate vaccine (initially PCV7, replaced by PCV13 in 2010) has been recommended by STIKO since

2006. Since then, a decline in IPD cases due to pneumococcal serotypes contained in PCV7/PCV13 has been observed not only in children but, through herd protection, also in older adults. Triggered by the approval of PCV13 for use in adults, STIKO investigated whether PCV13 or PPSV23 (or the combination of both) should be preferred for the vaccination of older adults and at what age the vaccine should be given.

Based on the meta-analysis of PPSV23 efficacy/effectiveness by Falkenhorst et al. [10] and the results of the PCV13 trial in the Netherlands [19], STIKO concluded that PPV23 continues to be the vaccine of choice for people aged 60 years or older. An important reason for this is the decrease of PCV13 serotypes among adults resulting from herd protection through routine infant immunization with PCV13. Due to the waning immunity, PPSV23 vaccination should be repeated every 6 years. Sequential vaccination with PCV13 followed by PPSV23 is only recommended for high-risk patients, i.e. people with immunocompromising conditions and those with a specific risk for pneumococcal meningitis. The evidence substantiating the updated recommendations for pneumococcal vaccination for older adults in Germany is presented in a background paper [25].

In Germany, IPD is not a mandatory notifiable disease, but there is a voluntary laboratory-based surveillance system in place (www.rki.de/pneumoweb). Data from this system indicates that serotypes included in PCV13 have decreased in all age groups over time, while serotypes not included in any vaccine are on the rise. Serotype 3 (included in PCV13) is unique in that it did not decline and now represents more than half of the remaining PCV13 serotypes. It has been postulated that this is due to the fact that serotype 3 strains are heavily encapsulated, inhibiting opsonisation. Once opsonized by antibodies, serotype 3 strains can even eject the polysaccharide together with the antibody and, as a result, escape phagocytosis [26–29]. It is legitimate to wonder whether it is even possible to achieve effective protection against serotype 3 with a vaccine based on its polysaccharide antigens.

Another question that arises is whether the usual distinction between IPD and pneumonia without bacteraemia is justified and useful. In the elderly, most cases of bacteraemia occur as a complication of pneumococcal pneumonia, while usually about 10–15% of pneumococcal pneumonia patients are diagnosed as having also bacteraemia. This percentage depends heavily on the frequency with which blood cultures are used. For example, in a patient with pneumococcal pneumonia, the disease will always be classified as non-bacteraemic, if no blood culture is taken. In patients with negative blood culture, it could be positive some hours later, or it could be negative, because the patient has already been put on antibiotic treatment.

Until recently, it was not possible to reliably determine the pneumococcal serotype from pneumococcal pneumonia patients with negative blood cultures. In this regard, a novel serotype-specific multiplex urinary antigen detection assay (SSUA) is a useful improvement. Pletz et al. [30] compared the serotype distribution in adult patients with pneumococcal CAP in Germany between the periods 2002–2006, i.e. before introduction of universal infant vaccination with PCV7 in late 2006, and 2007–2011. They reported a significant decrease in the proportion of PCV7 serotypes in adults with non-bacteraemic pneumococcal CAP (from 30.6% (2002–2006)

to 13.3% (2007–2011, $p < 0.001$), while PCV7 serotypes disappeared completely in bacteraemic pneumonia. Pneumococcal serotypes included in PCV13 remained stable during the study period. This is no surprise, because PCV13 replaced PCV7 in 2010 only, and it takes a few years for herd protection to take effect. Unfortunately, the SSUA assay detects only the 13 serotypes included in PCV13. An extension to the serotypes included in PPSV23 is highly desirable and would considerably improve the value of the assay for the monitoring of the epidemiological situation.

In this context of uncertainty regarding vaccine effectiveness and a proportion of probably only 20–30% of all CAP caused by *S. pneumoniae*, one might wonder what can reasonably be achieved with a pneumococcal vaccination programme for the elderly. To investigate this question, a dynamic transmission model and health economic analysis were developed by A. Kuhlmann et al. from the Center for Health Economics Research at Leibniz University in Hannover. The input parameters for the base case included a mixed serotype distribution in patients aged 60 years and over, with persistence of serotype 3; initial vaccine efficacy (with a waning curve) of 75% against VT-IPD and 66% against VT pneumococcal pneumonia for PPSV23 and, respectively, 77% and 46% for PCV13 and half these values for serotype 3; a duration of protection of 4.7 years against IPD and 3.8 years against pneumococcal pneumonia for PPSV23 and 8.2 years against both outcomes for PCV13; and vaccination uptake of 30%. They performed multiple sensitivity analyses, including a scenario with 0% efficacy of PPSV23 against PP.

The model predicts that a one-time vaccination with PPSV23 at age 60 averts about 3 times as many hospitalizations as a vaccination with PCV13. The number needed to vaccinate (NNV) to avoid one hospitalization is 801 for PPSV23 and 2490 for PCV13. Sequential vaccination with both vaccines would avert only marginally more hospitalizations than PPSV23 alone, while 6072 vaccinations with PCV13 would be needed to avert one additional hospitalization. Revaccination with PPSV23 every 6 years after initial vaccination with PPSV23 increases efficiency of the vaccination programme (NNV = 398), because the incidence of pneumococcal disease increases with age [31].

11.8 Communication and Vaccine Promotion

With a view to improving vaccine uptake, the “Impfen60+” (“Vaccinate60+”) campaign has been started in 2016 in the German federal state of Thuringia. It is a government-funded, trans-sectoral project bringing together medical science, epidemiology, communication science, psychology and design in order to improve vaccine uptake for flu and pneumococcal vaccination among adults aged 60–70 years. In addition to increasing vaccination uptake, other objectives include improving knowledge about sepsis and vaccination and reducing the incidence of flu, pneumonia and sepsis, thereby easing the burden on the healthcare system. The programme involves physicians, pharmacists, employers and local media, among others.

The communication strategy is based on the “5C model for vaccine hesitancy”, purporting that vaccine refusal can result from complacency, inconvenience, no

feeling of collective responsibility, lack of confidence and a rational calculation of the individual pros and cons of vaccination [32]. The programme spent one season on the evidence-based development of effective communication materials, taking into account the results of a representative survey on knowledge, attitudes and behaviours regarding flu vaccination and the use of different media among around 700 Thuringians aged 60–70 years of age. The campaign material was repeatedly pretested in that age group in order to ensure that their specific cognitive requirements are met.

11.9 Conclusions

Data from several countries have consistently shown that when high vaccination coverage with PCV13 in infants was achieved, serotypes contained in the PCV13 vaccine have markedly declined in all age groups due to herd protection from infant vaccination. With specific reference to the situation in Germany, in the 2015/2016 season, only about 30% of IPD cases in people aged 60 years and over were still caused by PCV13 serotypes, but about 70% by serotypes contained in PPSV23. This serotype mix, which appears to be similar in IPD and non-bacteraemic pneumonia, limits the potential impact of vaccinating elderly adults with PCV13. Based on our own critical review of the literature and meta-analyses, PPSV23 appears effective against both IPD and pneumococcal pneumonia and was therefore considered the better choice in Germany. However, the duration of protection is limited, with immunity waning over a period of about 5 years. Revaccination is crucial to maintain protection and achieve a meaningful impact at a population level. Activities to improve vaccination uptake should address specific cognitive and behavioural considerations of the target group for maximum effectiveness.

References

1. Feldman C, Anderson R. Bacteraemic pneumococcal pneumonia: current therapeutic options. Drugs. 2011;71(2):131–53.
2. Pneumococcal vaccines WHO position paper—2012. Wkly Epidemiol Rec. 2012;87(14):129–44.
3. Esposito S, Bonanni P, Maggi S, Tan L, Ansaldi F, Lopalco PL, et al. Recommended immunization schedules for adults: clinical practice guidelines by the Escmid Vaccine Study Group (EVASG), European Geriatric Medicine Society (EUGMS) and the World Association for Infectious Diseases and Immunological Disorders (WAidid). Hum Vaccin Immunother. 2016;12(7):1777–94.
4. European Centre for Disease Prevention and Control. Vaccine scheduler: pneumococcal disease: recommended vaccinations. https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=25&SelectedCountryIdByDisease=-1. Accessed 7 Mar 2018.
5. Government of Canada. Canadian immunization guide: part 4—active vaccines. Page 16: pneumococcal vaccine. 2016. https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-16-pneumococcal-vaccine.html#a9. Accessed 7 Mar 2018.

6. Tomczyk S, Bennett NM, Stoecker C, Gierke R, Moore MR, Whitney CG, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged >/=65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2014;63(37):822–5.
7. UK Department of Health. Interim JCVI statement on adult pneumococcal vaccination in the UK. 2015. https://www.gov.uk/government/publications/jcvi-interim-statement-on-adult-pneumococcal-vaccination. Accessed 14 Dec 2018.
8. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013;1:CD000422.
9. Walters JA, Tang JN, Poole P, Wood-Baker R. Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2017;1:CD001390.
10. Falkenhorst G, Remschmidt C, Harder T, Hummers-Pradier E, Wichmann O, Bogdan C. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV23) against pneumococcal disease in the elderly: systematic review and meta-analysis. PLoS One. 2017;12(1):e0169368.
11. Honkanen PO, Keistinen T, Miettinen L, Herva E, Sankilampi U, Laara E, et al. Incremental effectiveness of pneumococcal vaccine on simultaneously administered influenza vaccine in preventing pneumonia and pneumococcal pneumonia among persons aged 65 years or older. Vaccine. 1999;17(20–21):2493–500.
12. Örtqvist A, Hedlund J, Burman LA, Elbel E, Hofer M, Leinonen M, et al. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. Swedish pneumococcal vaccination study group. Lancet. 1998;351(9100):399–403.
13. Scott JA, Hall AJ, Leinonen M. Validation of immune-complex enzyme immunoassays for diagnosis of pneumococcal pneumonia among adults in Kenya. Clin Diagn Lab Immunol. 2000;7(1):64–7.
14. Musher DM, Mediwala R, Phan HM, Chen G, Baughn RE. Nonspecificity of assaying for IgG antibody to pneumolysin in circulating immune complexes as a means to diagnose pneumococcal pneumonia. Clin Infect Dis. 2001;32(4):534–8.
15. Maruyama T, Taguchi O, Niederman MS, Morser J, Kobayashi H, Kobayashi T, et al. Efficacy of 23-valent pneumococcal vaccine in preventing pneumonia and improving survival in nursing home residents: double blind, randomised and placebo controlled trial. BMJ. 2010;340:c1004.
16. Alfageme I, Vazquez R, Reyes N, Munoz J, Fernandez A, Hernandez M, et al. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. Thorax. 2006;61(3):189–95.
17. Remschmidt C, Harder T, Wichmann O, Bogdan C, Falkenhorst G. Effectiveness, immunogenicity and safety of 23-valent pneumococcal polysaccharide vaccine revaccinations in the elderly: a systematic review. BMC Infect Dis. 2016;16(1):711.
18. Jackson LA, Benson P, Sneller VP, Butler JC, Thompson RS, Chen RT, et al. Safety of revaccination with pneumococcal polysaccharide vaccine. JAMA. 1999;281(3):243–8.
19. Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015;372(12):1114–25.
20. van Werkhoven CH, Huijts SM, Bolkenbaas M, Grobbee DE, Bonten MJ. The impact of age on the efficacy of 13-valent pneumococcal conjugate vaccine in elderly. Clin Infect Dis. 2015;61(12):1835–8.
21. Rozenbaum MH, Pechlivanoglou P, van der Werf TS, Lo-Ten-Foe JR, Postma MJ, Hak E. The role of *Streptococcus pneumoniae* in community-acquired pneumonia among adults in Europe: a meta-analysis. Eur J Clin Microbiol Infect Dis. 2013;32(3):305–16.
22. Public Health England. Pneumococcal Polysaccharide Vaccine (PPV) coverage report, England, April 2016 to March 2017. Health Protection Report. 2017;11(23). https://www.gov.uk/government/publications/pneumococcal-polysaccharide-vaccine-ppv-vaccine-coverage-estimates. Accessed 28 Sept 2017.
23. Scientific Institute for Public Health. [Health survey 2013. Report 5: Prevention]. 2013. https://his.wiv-isp.be/nl/Gedeelde%20%20documenten/VA_NL_2013.pdf. Accessed 28 Sept 2017.

24. European Centre for Disease Prevention and Control. Immunisation schedules by target disease: Pneumococcal disease, All EU Countries. http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx. Accessed 14 Dec 2018.
25. Falkenhorst G, Remschmidt C, Harder T, Wichmann O, Glodny S, Hummers-Pradier E, et al. Background paper to the updated pneumococcal vaccination recommendation for older adults in Germany. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2016;59(12):1623–57.
26. Grabenstein JD, Musey LK. Differences in serious clinical outcomes of infection caused by specific pneumococcal serotypes among adults. Vaccine. 2014;32(21):2399–405.
27. Hammerschmidt S, Wolff S, Hocke A, Rosseau S, Muller E, Rohde M. Illustration of pneumococcal polysaccharide capsule during adherence and invasion of epithelial cells. Infect Immun. 2005;73(8):4653–67.
28. Sugimoto N, Yamagishi Y, Hirai J, Sakanashi D, Suematsu H, Nishiyama N, et al. Invasive pneumococcal disease caused by mucoid serotype 3 *Streptococcus pneumoniae*: a case report and literature review. BMC Res Notes. 2017;10(1):21.
29. Weinberger DM, Harboe ZB, Sanders EA, Ndiritu M, Klugman KP, Ruckinger S, et al. Association of serotype with risk of death due to pneumococcal pneumonia: a meta-analysis. Clin Infect Dis. 2010;51(6):692–9.
30. Pletz MW, Ewig S, Rohde G, Schuette H, Rupp J, Welte T, et al. Impact of pneumococcal vaccination in children on serotype distribution in adult community-acquired pneumonia using the serotype-specific multiplex urinary antigen detection assay. Vaccine. 2016;34(20):2342–8.
31. Kuhlmann A, Treskova M, Graf von der Schulenburg JM. [Pneumococcal disease in adults: health economic evaluation of different vaccine scenarios in Germany]. Full report in German. 2016. http://www.rki.de/DE/Content/Infekt/Impfen/Forschungsprojekte/abgeschlossene_Projekte/Pneumokokkenerkrankungen/Abschlussbericht.pdf?__blob=publicationFile. Accessed 30 Sept 2017.
32. Betsch C, Böhm R, Chapman GB. Using behavioral insights to increase vaccination policy effectiveness. Policy Insights Behav Brain Sci. 2015;2(1):61–73.

12 Direct and Indirect Benefits of a Comprehensive Approach to Vaccinating Adults with Influenza and Pneumococcal Vaccines, Especially in Patients with Chronic Diseases

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It is clear that there is a global ageing phenomenon. According to population estimates by the United Nations, 10% of the world's population was over 60 in 2000. This demographic segment will account for 15% of the overall population by 2025 and 21.8% by 2050, reaching a gross total of over two billion. There is no precedent for a society with this demographic structure, and there is an urgency to encourage health promotion and disease prevention. In this regard, immunization to reduce mortality and morbidity and improve quality of life is very important as we move forward to face the ageing challenge.

Globally, adult immunization faces many challenges. Paediatric vaccinations save an estimated two to three million lives each year [1], and many developed countries have well-established, robust childhood vaccination programmes. Initiatives, such as the Expanded Programme on Immunisation and the Global Alliance for Vaccines and Immunisation, are helping developing countries to build childhood immunization infrastructures and introduce new vaccines. However, worldwide, as in the United States, less attention has been paid to adult immunization, even in developed countries with strong public health infrastructures.

The global burden of adult vaccine-preventable disease (VPD) is considerable, and influenza (flu) and pneumococcal disease are major contributors to morbidity and mortality in older populations, with substantial burdens of death and disability around the world as assessed by disability-adjusted life years (DALYs), a metric that combines years lived with disability plus years of life lost. Globally, there is a

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_12

substantial burden of disease, with the sole caveat that there are not many reliable sources of data, especially for Africa and South East Asia.

A 2013 report commissioned by the SAATI (Supporting Active Ageing Through Immunisation) Partnership provides an overview of the state of adult immunization in 27 countries of the European Union (EU) and the value of implementing better immunization policies for the European adult population from a public health and macroeconomic perspective [2]. This report showed that during the 2010–2011 flu season in Europe, adults aged <65 years of age had the most severe disease, and most had underlying medical conditions (Fig. 12.1). Conversely, in the previous interpandemic period, adults older than 65 years with underlying conditions had the most severe disease, with considerable pressure on hospital and intensive care services in all countries. Regarding invasive pneumococcal disease (IPD), data from the report show that the groups at highest risk of contracting IPD include children, immunocompromised subjects and older people (>65 years of age). Indeed, the rates of reported confirmed IPD cases are highest among children <5 years and adults over 65. An improvement in the EU surveillance systems since 2010 has shown an increasing number of cases, and although mortality from IPD is low, pneumonia represents a major cause of death. Countries such as the United Kingdom have seen dramatic decreases in the number of cases thanks to the implementation of effective childhood immunization programmes, consequently benefitting adults through herd protection.

Focusing on the United States, the burden of adult VPD is similarly high. With a total of 29,500 cases and 3350 total deaths in the United States in 2015, 91% of IPD cases and nearly all IPD deaths occur in adults over 65 years of age [3]. Estimates of annual flu-associated deaths range from 3000 to 49,000, also affecting primarily older adults (65 years and over) [4]. There were a total of 20,762 reported cases of pertussis in the United States in 2015, of which 4650 were among adults aged 20 years and over [5]. Finally, there were an estimated 18,100 new hepatitis B infections in 2014 [6], and about one million cases of zoster occur per year in the United States [7].

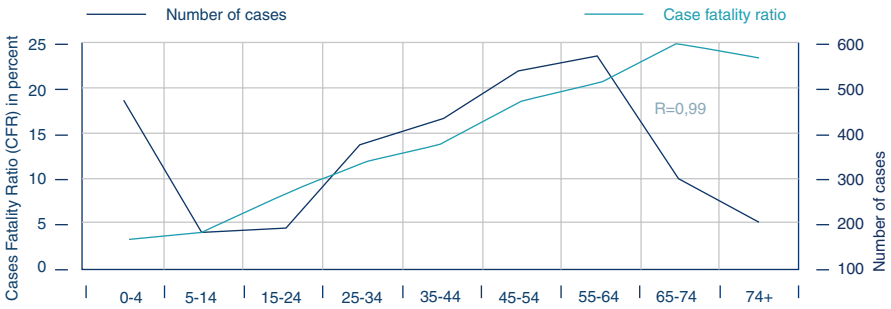

Fig. 12.1 Distribution of influenza-related severe acute respiratory infection cases and case-fatality ratio by age, EU/EEA countries, 2010–2011 season. From [2]

The estimated cost burden (both direct and indirect) from VPDs is also enormous, exceeding 15 billion USD annually for flu, pneumococcal disease, zoster and pertussis in those aged 65 years and over, plus another 11 billion USD annually if the 50–64-year age group is also considered [8].

Indirect effects of vaccination include aspects that are not often covered in clinical trials, namely, the prevention of the consequences of infection. For example, patients who suffer a VPD may be subsequently frailer and more prone to adverse health outcomes, resulting in a decline in functional status. For many seniors, the loss of quality of life is sometimes more important than concerns about mortality. When measuring vaccine effectiveness, there are challenges with measuring benefits from vaccination of the elderly. Some authors have reported that the benefits of vaccination may be overestimated in cohort studies due to frailty selection bias and the use of non-specific endpoints such as all-cause mortality [9]. Furthermore, people's personal health-seeking behaviours as well as opportunities for access to care also play a role, and the uptake of vaccination by preferentially healthy seniors can introduce a bias that is sufficient to account for the observed benefit [9–11], underlining the posit that better vaccines are needed to protect elderly patients who are particularly vulnerable to complications of influenza [12].

Regardless, ample evidence supports the need for vaccination strategy for adults. However, in order to justify, sustain and improve adult immunization programmes, we need to have systems that can monitor and measure the impact of these programmes—for example, on coverage rates. Surveillance systems from the European Union indicate that flu vaccine coverage rates in older age groups are well below target levels. Globally, it is hard to establish accurate coverage rates, because no systematic global data are available to assess vaccine provision or the effect of immunization policies. In this context, surrogate measures such as dose distribution have been used to estimate flu vaccine provision [13]. Results indicate that globally, vaccination rates are poor and stagnant, and not meeting WHO goals, except in certain regions where there is active management of the influenza programme. The situation is similar for pneumococcal vaccination. The WHO estimates global coverage at 37% [1], and while 21 EU countries have recommendations for vaccination of high-risk patients, of which 17 include elderly patients, only 3 countries provide coverage estimates. Yet without consistent and adequate surveillance of coverage rates, it is difficult to generate the data needed to justify moving policy forward into implementation. And without good surveillance data on the impact of disease, it can be hard to motivate countries to begin adult immunization programmes.

12.1 What Is the Impact of Vaccination?

12.1.1 Persons with Chronic Illness

A study by Kyaw et al. using 1999 and 2000 data from the Active Bacterial Core surveillance (ABCs) and the National Health Interview Survey (NHIS) showed that, as compared to healthy adults, the risk of IPD was increased three- to sevenfold in

patients with chronic conditions such as diabetes; chronic lung, heart, kidney or liver disease; and alcohol abuse [14]. They also observed a more than 20-fold increase in risk among patients with HIV/AIDS and in those with solid or haematological cancers, underlining the need for better prevention strategies in immunocompromised patients [14].

Flu-like illness has been found to be significantly associated with an increased risk of acute myocardial infarction, and flu vaccination effectiveness was estimated at 29% (95% CI, 9–44%), which is on a par with standard secondary prevention measures after acute myocardial infarction [15]. Similarly, in a meta-analysis of published randomized clinical trials, Udell et al. reported that the use of flu vaccine was associated with a significantly lower risk of major adverse cardiovascular events (risk ratio 0.64, 95% CI, 0.48–0.86, $p = 0.003$) [16]. Indeed, the American College of Cardiology/American Heart Association 2014 guidelines for the management of patients with non-ST-elevation acute coronary syndromes recommend annual flu vaccination for all patients with cardiovascular disease [17].

12.1.2 Pregnant Women

Among the groups at increased risk of adverse outcomes from influenza and flu-related illnesses, pregnant women have a fourfold higher risk of hospitalization, especially in the third trimester and in those with comorbid conditions [18]. The risk of influenza-associated complications, including death, is increased by up to eightfold in pregnant women, especially those with comorbid conditions such as diabetes mellitus, pulmonary disease (including asthma), heart disease, renal disease or anaemia. There is also an increased risk for the newborn infant of mothers with influenza during pregnancy, for adverse outcomes such as preterm birth or low birthweight, and infants <6 months old who develop flu infection have the highest rates of hospitalization and death among all children [18].

12.1.3 Those Over 65 Years of Age

Among elderly populations, chronic underlying diseases are more frequent, yet vaccine efficacy usually declines with increasing age. However, VPD incidence is such that there is a net benefit to vaccination overall [19].

Taken together, these data demonstrate that immunization across the lifespan is clearly beneficial to society. In this context, just as society committed to systematic childhood immunization in the twentieth century, due to its recognized benefit in the healthy growth of society, so we must now commit to adult immunization and embed it in healthy ageing initiatives for the coming century.

There are varying data regarding the effectiveness of various vaccines in adults. For example, data on the VE of the pneumococcal polysaccharide vaccine against non-bacteraemic pneumococcal pneumonia reports rates ranging from not effective at all to 28% for all-cause pneumonia and 50 to 80% for the prevention of IPD

among immunocompetent older adults or adults with various underlying illnesses [20–22]. Bonten et al. reported that VE of PCV13 was 45% against vaccine-type pneumococcal pneumonia and 75% against vaccine-type IPD in adults aged 65 years and older [23]. Between 1999 and 2016, at least ten different meta-analyses on PPV23 effectiveness were published, with widely inconsistent results [22, 24–31]. Regarding influenza, in an individual participant data meta-analysis on a total of 4975 patients, influenza vaccination was found to be significantly effective during epidemic seasons irrespective of vaccine match status, with a protective effect observed among elderly people with cardiovascular or lung disease [32]. Overall, data regarding the effectiveness of influenza vaccine are highly variable and depend on antigenic match, the age and health of the person being vaccinated.

Since vaccine effectiveness in adults is dependent on the outcome that is being measured, the success of an adult vaccination programme should not be measured solely by the outcome of incidence of disease prevented. Another way to look at vaccine effectiveness is to look at negative outcomes averted, and the benefit of flu vaccination in terms of vaccine-preventable disability is a weighty argument that appeals to people more easily than effectiveness statistics and may be a game changer for many older adults. Indeed, there is a high burden of VPDs in the elderly, particularly in terms of disability-adjusted life years (DALYs), which include years of life lost as well as years lived with disability. In a study from the Netherlands, Kristensen et al. showed that among older adults, the disease burden in the period 2010–2013 in terms of DALYs was highest for pneumococcal disease, mostly because of high mortality, followed by influenza [33].

Herd protection is an important indirect effect of vaccination, with a particularly major role for children and youngsters. A cluster randomized trial involving 947 Canadian children and adolescents aged 36 months to 15 years who received influenza vaccine and 2326 unvaccinated community members reported a protective effectiveness of 61% (95% CI, 8–83%; $P = 0.03$), showing that immunization of children and adolescents significantly protected unimmunized residents of rural communities against influenza [34]. Similarly, data from observational studies have shown a significant reduction in influenza illness in contacts of vaccinated patients (OR 0.57; 95% CI, 0.43–0.77) [35], although no significant association was observed in randomized studies in the same meta-analysis. It is likely that variability by season, vaccine coverage and circulating strains, as well as difficulties in monitoring outpatient illness among adult contacts, render accurate evaluations of herd effect challenging in the community.

Nonetheless, once the evidence in favour of vaccination is convincing, it is necessary to implement strong policies that commit to vaccination. The US adult immunization schedule recommends flu vaccination for all persons aged 6 months and older, once a year, and recommends pneumococcal vaccine for all those aged 65 years and older (PCV13 and PPSV23, one dose of each). There is a scientific rationale for encouraging concomitant vaccination with flu and pneumococcal vaccines, as pneumococcal infections increase with spikes in influenza disease [36]. Furthermore, pneumococcal infection secondary to influenza disease predicts more severe outcomes and increased deaths in the elderly, with almost 90% of annual

deaths with underlying pneumonia and flu causes occurring in persons older than 65 years and accounting for excess mortality during flu epidemics [37]. Similarly, secondary bacterial pneumonia (mostly *S. pneumoniae*) is estimated to account for up to 50% of deaths during seasonal flu in the United States, due to the damaged caused to the airway epithelium by influenza, and enhanced bacterial colonization due to reduced clearance [38]. Co-administration of influenza and pneumococcal vaccines has been found to have greater cost-effectiveness. In a review of the literature, Gilchrist et al. showed that eight of nine clinical studies found that a concomitant programme conferred clinical benefits, while the two studies that compared the cost-effectiveness of different strategies found concomitant immunization to be more cost-effective than either vaccine given alone [39]. Co-administration has also been shown to be safe, in terms of adverse reactions [40].

The broad potential impact of influenza and pneumococcal vaccination in adults is therefore clear, and vaccines are available that are shown to be effective. In this context, any impact of vaccines is dependent on improving coverage rates and public awareness, as well as improving clinicians' willingness to give the vaccine, the public's ability to get access to vaccines (payment/cost policies) and improving surveillance of disease and availability of data on the impact of vaccines and vaccination.

References

1. Immunization coverage factsheet. 2017. http://www.who.int/mediacentre/factsheets/fs378/en/. Accessed 04 Oct 2017.
2. SAATI Partnership. Adult vaccination: a key component of healthy ageing. The benefits of life-course immunisation in Europe. 2013. http://www.ilcuk.org.uk/images/uploads/publication-pdfs/Adult_vaccination_-_a_key_component_of_health_ageing.pdf. Accessed 04 Oct 2017.
3. Centers for Disease Control and Prevention. Bacterial Core Surveillance Report, Emerging Infections Program Network, Streptococcus pneumoniae. http://www.cdc.gov/abcs/reports-findings/survreports/spneu15.pdf. Accessed 04 Oct 2017.
4. Centers for Disease C, Prevention. Estimates of deaths associated with seasonal influenza—United States, 1976–2007. MMWR Morb Mortal Wkly Rep. 2010;59(33):1057–62.
5. Centers for Disease Control and Prevention. 2015 Final Pertussis Surveillance Report. https://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2015.pdf. Accessed 04 Oct 2017.
6. Centers for Disease Control and Prevention. Surveillance for Viral Hepatitis—United States. 2014. https://www.cdc.gov/hepatitis/statistics/2014surveillance/pdfs/2014HepSurveillanceRpt_Rev2016-09-26.pdf. Accessed 04 Oct 2017.
7. Harpaz R, Ortega-Sanchez IR, Seward JF, Advisory Committee on Immunization Practices Centers for Disease C, Prevention. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2008;57(RR-5):1–30; quiz CE2-4.
8. McLaughlin JM, McGinnis JJ, Tan L, Mercatante A, Fortuna J. Estimated human and economic burden of four major adult vaccine-preventable diseases in the United States, 2013. J Prim Prev. 2015;36(4):259–73.
9. Simonsen L, Taylor RJ, Viboud C, Miller MA, Jackson LA. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. Lancet Infect Dis. 2007;7(10):658–66.

10. Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. Int J Epidemiol. 2006;35(2):337–44.
11. Jackson LA, Nelson JC, Benson P, Neuzil KM, Reid RJ, Psaty BM, et al. Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. Int J Epidemiol. 2006;35(2):345–52.
12. Glezen WP, Simonsen L. Commentary: benefits of influenza vaccine in US elderly–new studies raise questions. Int J Epidemiol. 2006;35(2):352–3.
13. Palache A. Seasonal influenza vaccine provision in 157 countries (2004–2009) and the potential influence of national public health policies. Vaccine. 2011;29(51):9459–66.
14. Kyaw MH, Rose CE Jr, Fry AM, Singleton JA, Moore Z, Zell ER, et al. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. J Infect Dis. 2005;192(3):377–86.
15. Barnes M, Heywood AE, Mahimbo A, Rahman B, Newall AT, Macintyre CR. Acute myocardial infarction and influenza: a meta-analysis of case-control studies. Heart. 2015;101(21):1738–47.
16. Udell JA, Zawi R, Bhatt DL, Keshtkar-Jahromi M, Gaughran F, Phrommintikul A, et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. JAMA. 2013;310(16):1711–20.
17. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64(24):e139–228.
18. Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. Am J Obstet Gynecol. 2012;207(Suppl. 3):S3–8.
19. Gessner BD, Feikin DR. Vaccine preventable disease incidence as a complement to vaccine efficacy for setting vaccine policy. Vaccine. 2014;32(26):3133–8.
20. Leventer-Roberts M, Feldman BS, Brufman I, Cohen-Stavi CJ, Hoshen M, Balicer RD. Effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive disease and hospital-treated pneumonia among people aged >/=65 years: a retrospective case-control study. Clin Infect Dis. 2015;60(10):1472–80.
21. Dominguez A, Soldevila N, Toledo D, Torner N, Force L, Perez MJ, et al. Effectiveness of 23-valent pneumococcal polysaccharide vaccination in preventing community-acquired pneumonia hospitalization and severe outcomes in the elderly in Spain. PLoS One. 2017;12(2):e0171943.
22. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013;1:CD000422.
23. Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015;372(12):1114–25.
24. Cornu C, Yzebe D, Leophonte P, Gaillat J, Boissel JP, Cucherat M. Efficacy of pneumococcal polysaccharide vaccine in immunocompetent adults: a meta-analysis of randomized trials. Vaccine. 2001;19(32):4780–90.
25. Hutchison BG, Oxman AD, Shannon HS, Lloyd S, Altmayer CA, Thomas K. Clinical effectiveness of pneumococcal vaccine. Meta-analysis. Canadian family physician Medecin de famille canadien, vol. 45; 1999. p. 2381–93.
26. Melegaro A, Edmunds WJ. The 23-valent pneumococcal polysaccharide vaccine. Part I. Efficacy of PPV in the elderly: a comparison of meta-analyses. Eur J Epidemiol. 2004;19(4):353–63.
27. Schiffner-Rohe J, Witt A, Hemmerling J, von Eiff C, Leverkus FW. Efficacy of PPV23 in preventing pneumococcal pneumonia in adults at increased risk—a systematic review and meta-analysis. PLoS One. 2016;11(1):e0146338.
28. Kraicer-Melamed H, O'Donnell S, Quach C. The effectiveness of pneumococcal polysaccharide vaccine 23 (PPV23) in the general population of 50 years of age and older: a systematic review and meta-analysis. Vaccine. 2016;34(13):1540–50.

29. Conaty S, Watson L, Dinnes J, Waugh N. The effectiveness of pneumococcal polysaccharide vaccines in adults: a systematic review of observational studies and comparison with results from randomised controlled trials. Vaccine. 2004;22(23–24):3214–24.
30. Huss A, Scott P, Stuck AE, Trotter C, Egger M. Efficacy of pneumococcal vaccination in adults: a meta-analysis. CMAJ. 2009;180(1):48–58.
31. Diao WQ, Shen N, Yu PX, Liu BB, He B. Efficacy of 23-valent pneumococcal polysaccharide vaccine in preventing community-acquired pneumonia among immunocompetent adults: a systematic review and meta-analysis of randomized trials. Vaccine. 2016;34(13):1496–503.
32. Darvishian M, van den Heuvel ER, Bissielo A, Castilla J, Cohen C, Englund H, et al. Effectiveness of seasonal influenza vaccination in community-dwelling elderly people: an individual participant data meta-analysis of test-negative design case-control studies. Lancet Respir Med. 2017;5(3):200–11.
33. Kristensen M, van Lier A, Eilers R, McDonald SA, Opstelten W, van der Maas N, et al. Burden of four vaccine preventable diseases in older adults. Vaccine. 2016;34(7):942–9.
34. 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.
35. Mertz D, Fadel SA, Lam PP, Tran D, Srigley JA, Asner SA, et al. Herd effect from influenza vaccination in non-healthcare settings: a systematic review of randomised controlled trials and observational studies. Euro Surveill. 2016;21(42).
36. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J Infect Dis. 2008;198(7):962–70.
37. Centers for Disease Control and Prevention (CDC). Estimates of deaths associated with seasonal influenza—United States, 1976–2007. MMWR Morb Mortal Wkly Rep. 2010;59(33):1057–62.
38. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. Clin Microbiol Rev. 2006;19(3):571–82.
39. Gilchrist SA, Nanni A, Levine O. Benefits and effectiveness of administering pneumococcal polysaccharide vaccine with seasonal influenza vaccine: an approach for policymakers. Am J Public Health. 2012;102(4):596–605.
40. Honkanen PO, Keistinen T, Kivela SL. Reactions following administration of influenza vaccine alone or with pneumococcal vaccine to the elderly. Arch Intern Med. 1996;156(2):205–8.

Vaccination of Healthcare Professionals and Protection of Hospitalized Adults and Nursing Home Residents

13

Gaetan Gavazzi

Vaccination is a topic that has long been the subject of debate, and this debate covers both individual and collective issues. At the individual level, there is primarily the individual's perception of the efficacy of vaccines and their potential to give rise to adverse reactions. In addition, public opinion regarding vaccination is strongly influenced by media coverage, sensational news stories and anecdotal evidence. However, at collective level, like most public health challenges, vaccination policy is dependent on overall public health policies, in particular taking account of the cost-effectiveness ratio and the measure of the individual versus the collective interest [1].

In the United States, the Advisory Committee on Immunization Practices recommends that all healthcare workers (HCWs) be vaccinated annually against influenza (flu). From an opt-in Internet panel survey of 1882 HCW conducted in April 2014 to estimate flu vaccination coverage among HCW during the 2013–2014 season, the Center for Disease Control (CDC) found that, overall, 75.2% of participating HCW reported receiving an influenza vaccination during the 2013–2014 season. Interestingly, HCW working in settings where vaccination was required had higher coverage (97.8%) compared with those working in settings where flu vaccine was not required but promoted (72.4%) or settings where there was no requirement or promotion of vaccination (47.9%).

In France, mandatory vaccines are taken up by over 90%, underlining that target vaccination can be reached when vaccination is obligatory. In a national cross-sectional survey among 452 HCWs working in clinics and hospitals in France, vaccination coverage was found to be over 90% for compulsory vaccines such as

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_13

hepatitis B, diphtheria-tetanus-polio and BCG. Conversely, when vaccination was only recommended, uptake was found to be very low, ranging from 49.7% for at least one dose of measles to as low as 11.4% for the booster of the DTP pertussis-containing vaccine [2].

There is a clear rationale for vaccinating HCW. Firstly, they are in regular close contact with numerous microorganisms, and therefore, protecting them against the work-related infectious risk from vaccine-preventable diseases (VPDs) is justified. In addition, through their contact with pathogens, they constitute a reservoir for ongoing transmission to subsequent patients in contact with that HCW for whom infection could pose a serious health threat. Therefore, vaccination of HCW also serves to protect patients from nosocomial transmission of VPDs via herd immunity [3].

While this equation may appear simple, its implementation is challenging. Indeed, there are a range of different risks and types of transmission, with different attack rates between diseases. Therefore, finding a vaccination strategy that fits every setting is particularly complex. Hepatitis B is an illustrative example. The prevalence of hepatitis B is around 0.1 to 20% worldwide and <2% in Europe [4, 5]. Yet, in Europe, direct or indirect contamination from patients to HCW or vice versa is very rare. Thus, the goal is to protect HCW and a low number of patients in care situations (e.g. surgery). However, the major difference underpinning vaccination practices is the perception of the disease. Indeed, hepatitis B is perceived as a harmful disease, whereas the flu is not considered to be dangerous. Yet, in 2014–2015, there were 410 outbreaks and, in 2017, more than 800 outbreaks and more than 20,000 excess deaths in the flu season. Flu may not be directly responsible for all these deaths but contributes at least partially. In addition, one must also consider the collateral burden represented by the disability induced by flu, which is often not taken into account. The estimations of flu-related deaths also have to be interpreted in the context of a comparison to the normal rate of death outside of the flu season, which may be unknown or fluctuating. Despite these uncertainties, it remains clear that influenza infections are more common among HCW than in the common population with attack rates ranging from 13% to 23%. HCW may be responsible for 10–50% of outbreaks among nosocomial outbreaks, since they are often asymptomatic in the first days of infection, and death rates from nosocomial flu reportedly vary from 5% to 60%.

In summary, there is a clear rationale for vaccinating personnel working in the healthcare system, primarily for their own protection against the acquisition from patients of vaccine-preventable diseases such as hepatitis. The goal is thus to decrease absenteeism and loss of productivity from illness among the HCWs, to prevent further spread of the disease to colleagues and, more importantly, to prevent the onward transmission to patients of infections such as flu, measles, pertussis, varicella or mumps. Reducing nosocomial infection in turn helps to minimize the length of stay, medical costs and potential risk of mortality. In this regard, both HCW and patients are affected by VPDs within the healthcare system, but they are affected at different levels, with different levels of risk according to the season. The vaccination of HCWs represents the front line of this battle. This is particularly

important for diseases such as pertussis, where immunity among the general population is low because of insufficient vaccine coverage among children, combined with waning immunity among the elderly. There is therefore a substantial risk of transmission from HCW to patient, and outbreaks in the hospital or other healthcare settings, although sporadic, generate significant morbidity, physical and emotional stress and are resource-intensive and disruptive for the institution concerned [6].

In this context, are there efficient vaccines available to protect HCWs? Undoubtedly, the answer is a resounding yes. Inactivated flu vaccines are 50–70% efficacious in preventing influenza-like illness (ILI) among healthy adults, and vaccination among HCWs has been shown to reduce absenteeism [3, 7, 8]. Adverse drug reactions may occur and include tenderness, pain and fever, while neurological disorders remain extremely rare with a frequency of <1/10,000.

Mortality in nursing home residents decreases with increasing vaccination of HCWs, regardless of the vaccine status of the residents or their functional status. In a study by Carman et al. [9], HCW in 20 long-term residential nursing homes were randomly offered vaccination or not in a cluster-randomized design stratified for the policy for vaccination of residents. They reported that vaccine uptake was 50.9% in hospitals where vaccination was routinely offered versus only 4.9% when it was not routinely proposed. In addition, there was a significant decrease in uncorrected mortality rates in vaccine hospitals (13.6% death rate) compared with no-vaccine hospitals (22.4%) (OR 0.58, 95% CI: 0.40–0.84, $p = 0.014$), indicating that vaccination of HCW is associated with a significant decrease in mortality among patients. Similarly, in a pair-matched, cluster-randomized trial in large private chain of UK care homes conducted over two winter periods of influenza circulation, Hayward et al. [10] reported that vaccination uptake was 48.2% (407/884) in intervention nursing homes and 5.9% (51.859) in control establishments for the 2003–2004 season and, respectively, 43.2% (365/844) and 3.5% (28/800) in 2004–2005. In the 2003–2004 period of intense influenza activity, there was a significant decrease in mortality among residents in the intervention nursing homes, compared to control homes (5 fewer deaths per 100 residents in intervention compared to control homes—95% CI: 2–7, $p = 0.002$), and a significant reduction in influenza-like illness ($p = 0.004$), again underlining that vaccinating nursing home staff against influenza can prevent deaths among residents. Similarly, a third cluster-randomized trial by Lemaitre et al. [11] among 40 nursing homes reported vaccination uptake of 69.9% in the intervention arm (comprising influenza vaccination with volunteer staff after a face-to-face interview), versus 31.8% in the control arm (no intervention). Although in this study, primary unadjusted analysis did not show significantly lower mortality in residents in the vaccination arm (OR = 0.86, $P = 0.08$), adjusted multivariate analysis showed 20% lower mortality ($P = 0.02$) and a strong correlation between staff vaccination coverage and all-cause mortality in residents (correlation coefficient = −0.42, $P = 0.007$). Furthermore, in the vaccination arm, the rate of influenza-like illness in residents was 31% lower ($P = 0.007$), and sick leave from work in staff was 42% lower ($P = 0.03$), supporting a benefit of vaccination among staff caring for elderly patients in nursing homes, independently of the residents' vaccination status or functional status.

Surprisingly, two Cochrane systematic reviews published at 3 years interval failed to find conclusive evidence of benefit of HCW vaccination programmes on specific outcomes of laboratory-proven influenza, its complications or all-cause mortality in people aged over 60 living in long-term care institutions [12, 13]. The discrepancies in these findings may be due to the fact that the systematic reviews by Thomas et al. did not necessarily consider the primary endpoints reported in the individual trials included in the review, and the risk of bias in methodology led the authors of the review to downgrade some of the evidence coming from the individual trials included. Therefore, Thomas et al. conclude that further high-quality randomized controlled trials are required to test the efficacy of vaccination and other combinations of hygiene and prevention measures.

All the trials mentioned above were performed in the setting of long-term care, but it is almost impossible to perform studies (and definitely not RCTs) about the efficiency of vaccines in other wards over the flu season. Indeed, it is hard to distinguish the contribution of HCW vaccination in protecting patients. In high-risk wards, at least, nosocomial influenza may occur in 20–60%, despite other strategies, such as hygiene, handwashing, masks, etc. There may also exist a link between vaccine programmes and reductions in nosocomial flu infections. Indeed, in an 8-year study, Frenzel et al. [14] found that a multifaceted approach including mandatory influenza vaccination significantly improved vaccine uptake rates among the targeted HCWs and led to a reduction in the proportion of nosocomial influenza infections in immunocompromised cancer patients.

However, vaccine uptake varies among HCWs in nursing homes and may vary especially from year to year, as a result of public health campaigns, introduction of mandatory vaccine programmes or other measures. Several reports relaying vaccination coverage rates for VPDs such as influenza, hepatitis B and measles show alarmingly low uptake rates [15, 16]. For the flu vaccine in particular, rates range from 0% in Norway to 18% in Ireland through 33.6% in France and up to 85% in Japan [15–20]. Indeed, there are wide discrepancies across countries in terms of recommended vaccines, indications and legislative frameworks, and even now, there are countries in Europe where no vaccination policy is in place for HCWs [21]. Mandatory status for vaccination is rare, and most countries only have recommendations in place, often for specific subgroups of the population. Yet, this wide variability in practices is not explained by any specific different background for many of the vaccines concerned.

In view of the mediocre uptake rates and varying policies, one might wonder what barriers prevent people, particularly HCWs, from receiving vaccination. These may include individual reasons relating to the flu vaccine, such as a lack of time and/or motivation, a perceived lack of efficacy of the vaccine, fear of the injection itself or adverse effects, reported alternative protection such as homeopathy, etc. [22]. Other reasons may relate to the disease itself. First and foremost among these is the idea that influenza is not a serious disease. Other misconceptions include the idea that it is only problematic in frail individuals, or that it is not contagious, or there is a low risk of nosocomial transmission [22]. In addition, organizational factors may play a role, for example, the cost (if borne by the HCW), the general

inconvenience or a lack of access to flu shots in the workplace [22, 23]. Indeed, occupational medicine may be the responsibility of different organisms across different countries, and in some places, there may be no systematic occupational medicine follow-up or no provisions for systematic flu vaccination through occupational medicine services. Therefore, in practical terms, we have to think about how can we reach HCWs to implement vaccination, across specialties and among different types of HCWs, since practices are different between disciplines. In this regard, Landelle et al. reported in their study of flu vaccine coverage among patients and HCWs in four wards of a large university hospital that physicians were significantly more likely to be vaccinated than the rest of staff (adjusted OR 8.29, 95% CI: 1.58–43.41), while residents and staff from the geriatrics unit were more likely to be vaccinated, albeit without reaching statistical significance [24].

The determinants of vaccination uptake are multifactorial. Paterson et al. performed a review of 185 articles in the literature dealing with vaccine hesitancy among HCWs and the influence of their own vaccine confidence or vaccination behaviour on their recommendations to others [25]. Overall, they found that increased knowledge about vaccines, their efficacy and their safety helped to build confidence among HCWs, thus increasing their willingness to recommend vaccination to others. Endorsement from influential leaders and individuals and societal and colleague support were also found to be important vectors for building combating vaccine reluctance. This is important, because HCWs remain the most trusted influencers of vaccine decisions among patients, who look to their healthcare provider for advice and guidance in this regard [25]. HCWs must be sufficiently well informed to be able to respond adequately to the questions of patients, particularly in the face of the growing anti-vaccine public.

In an effort to identify and address the determinants of reluctance for vaccination in nursing homes, our group performed a programme of education and communication over three seasons (the VESTA study) [26, 27]. The programme included identification of the factors determining vaccination reluctance, followed by an education programme and a communication campaign. Between June and September 2005, 2485 HCWs (vaccination coverage: 23.4%) from 53 French geriatric units were included in the study. Cluster analysis determined three composite profiles, namely, HCWs for whom information programmes on vaccination can be useful (59%), those who were staunchly opposed to vaccination (36%), and those were sceptical (5%) [26, 27]. Finding that the flu vaccine had a very bad image among the participants in the programme, we constructed an educational programme to take action against this particular point. After the failure of a first educational programme giving scientific information, a second programme was designed with the help of marketing experts, 1 year after Programme 1. The objectives were to involve HCWs in the creation of "safety zones" and to give personal satisfaction. Programme 2 was tested during the 2006–2007 influenza season; 20 of the 24 healthcare settings from the Programme 1 cluster were included in Programme 2, totalling 1814 HCWs, and 23 healthcare settings totalling 2435 HCWs were included in the Control 2 cluster. Whereas Programme 1 had failed to increase HCW vaccination coverage (Programme 1: 34%; Control 1: 32%; $p > 0.05$), Programme 2 increased the vaccine

coverage rates among HCWs (Programme 2: 44%; Control 2: 27%; $p < 0.001$), regardless of their occupational group, but only in the non-previously vaccinated subgroup [26, 27]. Indeed, while the rate of vaccination remained relatively stable among previously vaccinated HCWs, it increased twofold in the group of those who were previously unvaccinated over the whole programme duration [27]. Overall, these programmes revealed that there must be some incentive and acknowledgement of a positive attitude towards vaccination, and education alone via the provision of scientifically factual information is clearly not sufficient. A programme that yields personal satisfaction and takes account of the specificities of non-vaccinated HCWs is more effective in obtaining good adherence and avoiding rejection of top-down hierarchical recommendations for vaccination.

Communication is key in this regard, and potentially useful approaches include the use of leaflets and posters, information campaigns by key opinion leaders, intensive vaccination campaigns including incentives for those who comply and simplified organizational access to vaccine shots, e.g. through mobile vaccination teams [16, 28, 29]. Educational programmes aimed at improving knowledge about vaccines and dispelling myths and misconceptions can also be implemented. However, despite the numerous possibilities for short-term actions to achieve efficacy, the results are short-lived. For long-term efficacy, long-term plans are required. In the United States, Nace et al. conducted a needs analysis to determine the organizational and individual level barriers to influenza vaccination of staff in long-term care facilities. Using data from 1996 to 1997 as baseline, they reported that staff immunization rates improved from around 55% to between 74% and 95% over 4 years, through the implementation of systems changes, educational interventions and reminders under the leadership of an involved quality improvement team and medical director [28]. Indeed, long-term programmes are fundamental to achieving a cultural shift in the paradigm that can lead to definitive changes in behaviour.

One simple and rapid means to achieve high vaccine uptake rates within a very short time is to make vaccination mandatory. Talbot et al. reported that immunization rates among HCWs ranged from 50 to around 90% the year prior to implementation of a mandatory vaccination programme at selected health institutions, whereas all establishments displayed rates in excess of 95% up to almost 100% the year after the mandate [30]. It should be noted however that all “mandatory vaccination” programmes are not the same, with variations in the actual requirements and the penalties for non-compliance. Indeed, the highest rates of compliance are observed in institutions where there are consequences for non-compliance [31]. Other approaches for achieving higher vaccine uptake rates among HCWs, including declination forms and requirements for mask use among unvaccinated HCWs, have shown varying efficacy [32, 33].

Mandatory vaccination policies are fraught with a number of ethical issues. Arguments in favour of mandatory vaccination include the fact that influenza, for example, is a highly prevalent disease with a substantial impact. However, evidence is more equivocal as regards the potential benefit of HCW vaccination and the achievement of herd immunity with this policy. It would seem logical that such would be the situation in nursing homes, for example, where the population is frail

and their main contact is with HCWs, but two Cochrane reviews provide evidence to the contrary [12, 13]. Similarly, to justify mandatory vaccination, we need to have observed a failure of voluntary programmes, and here again, the evidence in this regard is unconvincing, and voluntary programmes may take several years to yield results, making it difficult to conclude regarding their efficacy. Arguments against mandatory vaccination are largely based on the principle of HCW autonomy, but there is ongoing debate as to whether the importance of HCW autonomy counterbalances the deleterious effects of disease, the failure of voluntary programmes and the lack of political will from public health institutions.

In conclusion, at a scientific level, there is a compelling need to clearly determine the burden of influenza disease and to better explain the high variability between flu seasons and in the impact on patients. In this regard, HCW vaccination will impact differently in place and in time. At an organizational/institutional level, there was an urgent need for clear European guidance for HCW vaccination, and this has now been achieved since the publication in 2016 of clinical practice guidelines from the ESCMID Vaccine Study Group (EVASG), the European Geriatric Medicine Society (EUGMS) and the World Association for Infectious Diseases and Immunological Disorders (WAidid) [34]. To achieve a harmonious policy suitable for implementation across Europe, with its highly variable healthcare systems, it is necessary to determine who will provide the vaccine, who will control the vaccination uptake and who are the target populations. Among HCWs in particular, there remains a lack of knowledge regarding the issues surrounding vaccination, but acquiring knowledge is complex in this population. Implementing multidimensional programmes adapted to each disease or vaccine is possible, but this solution is time-consuming and costly and demands strong political will and financial support, although it can lead to a durable shift in culture. Mandatory vaccination is cheaper and quicker but requires political will in order to be activated, and there may be ethical issues involved that could give rise to debate and/or reluctance at local, national or international levels.

In the meantime, while these questions remain unresolved, it should be remembered that prevention is also a whole set of basic actions that can be implemented everywhere, by everyone, and without raising ethical issues: handwashing, face masks, early detection of laboratory-proven flu, quarantine of units, avoiding new admissions, prompt use of antivirals and eviction of workers with infection.

References

1. Balinska MA. What is vaccine advocacy? Proposal for a definition and action. Vaccine. 2004;22:1335–42.
2. Guthmann JP, Fonteneau L, Ciotti C, et al. Vaccination coverage of health care personnel working in health care facilities in France: results of a national survey, 2009. Vaccine. 2012;30:4648–54.
3. Sydnor E, Perl TM. Healthcare providers as sources of vaccine-preventable diseases. Vaccine. 2014;32:4814–22.
4. European Centre for Disease Prevention and Control. Systematic review on hepatitis B and C prevalence in the EU/EEA. Stockholm: ECDC; 2016.

5. MacLachlan JH, Cowie BC. Hepatitis B virus epidemiology. Cold Spring Harb Perspect Med. 2015;5:a021410.
6. Heininger U. Vaccination of health care workers against pertussis: meeting the need for safety within hospitals. Vaccine. 2014;32:4840–3.
7. Maltezou HC. Nosocomial influenza: new concepts and practice. Curr Opin Infect Dis. 2008;21:337–43.
8. Wilde JA, McMillan JA, Serwint J, et al. Effectiveness of influenza vaccine in health care professionals: a randomized trial. JAMA. 1999;281:908–13.
9. Carman WF, Elder AG, Wallace LA, et al. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. Lancet. 2000;355:93–7.
10. Hayward AC, Harling R, Wetten S, et al. Effectiveness of an influenza vaccine programme for care home staff to prevent death, morbidity, and health service use among residents: cluster randomised controlled trial. BMJ. 2006;333:1241.
11. Lemaitre M, Meret T, Rothan-Tondeur M, et al. Effect of influenza vaccination of nursing home staff on mortality of residents: a cluster-randomized trial. J Am Geriatr Soc. 2009;57:1580–6.
12. Thomas RE, Jefferson T, Lasserson TJ. Influenza vaccination for healthcare workers who care for people aged 60 or older living in long-term care institutions. Cochrane Database Syst Rev. 2013:CD005187.
13. Thomas RE, Jefferson T, Lasserson TJ. Influenza vaccination for healthcare workers who care for people aged 60 or older living in long-term care institutions. Cochrane Database Syst Rev. 2016:CD005187.
14. Frenzel E, Chemaly RF, Ariza-Heredia E, et al. Association of increased influenza vaccination in health care workers with a reduction in nosocomial influenza infections in cancer patients. Am J Infect Control. 2016;44:1016–21.
15. Fiebelkorn AP, Seward JF, Orenstein WA. A global perspective of vaccination of healthcare personnel against measles: systematic review. Vaccine. 2014;32:4823–39.
16. FitzSimons D, Hendrickx G, Lernout T, et al. Incentives and barriers regarding immunization against influenza and hepatitis of health care workers. Vaccine. 2014;32:4849–54.
17. Bentele H, Bergsaker MR, Hauge SH, et al. Vaccination coverage for seasonal influenza among residents and health care workers in Norwegian nursing homes during the 2012/13 season, a cross-sectional study. BMC Public Health. 2014;14:434.
18. Ishikane M, Kamiya H, Kawabata K, et al. Seasonal influenza vaccine (A/New York/39/2012) effectiveness against influenza a virus of health care workers in a long term care facility attached with the hospital, Japan, 2014/15: a cohort study. J Infect Chemother. 2016;22:777–9.
19. O'Lorcain P, Cotter S, Hickey L, et al. Seasonal influenza vaccine uptake in HSE-funded hospitals and nursing homes during the 2011/2012 influenza season. Ir Med J. 2014;107:74–7.
20. Vaux S, Noel D, Fonteneau L, et al. Influenza vaccination coverage of healthcare workers and residents and their determinants in nursing homes for elderly people in France: a cross-sectional survey. BMC Public Health. 2010;10:159.
21. Maltezou HC, Poland GA. Immunization of healthcare providers: a critical step toward patient safety. Vaccine. 2014;32:4813.
22. Gavazzi G. Influenza vaccination for healthcare workers: from a simple concept to a resistant issue? Aging Clin Exp Res. 2009;21:216–21.
23. Aubert M, Aumaitre H, Beytout J, et al. Current events in vaccination. Med Mal Infect. 2011;41:278–90.
24. Landelle C, Vanhems P, Saadatian-Elahi M, et al. Influenza vaccination coverage among patients and healthcare workers in a university hospital during the 2006–2007 influenza season. Vaccine. 2012;31:23–6.
25. Paterson P, Meurice F, Stanberry LR, et al. Vaccine hesitancy and healthcare providers. Vaccine. 2016;34:6700–6.
26. Gavazzi G, Filali-Zegzouti Y, Guyon AC, et al. French healthcare workers in geriatric healthcare settings staunchly opposed to influenza vaccination: the VESTA study. Vaccine. 2011;29:1611–6.

27. Rothan-Tondeur M, Filali-Zegzouti Y, Golmard JL, et al. Randomised active programs on healthcare workers' flu vaccination in geriatric health care settings in France: the VESTA study. J Nutr Health Aging. 2011;15:126–32.
28. Nace DA, Hoffman EL, Resnick NM, et al. Achieving and sustaining high rates of influenza immunization among long-term care staff. J Am Med Dir Assoc. 2007;8:128–33.
29. Salgado CD, Giannetta ET, Hayden FG, et al. Preventing nosocomial influenza by improving the vaccine acceptance rate of clinicians. Infect Control Hosp Epidemiol. 2004;25:923–8.
30. Talbot TR. Update on immunizations for healthcare personnel in the United States. Vaccine. 2014;32:4869–75.
31. Nowalk MP, Lin CJ, Raymund M, et al. Impact of hospital policies on health care workers' influenza vaccination rates. Am J Infect Control. 2013;41:697–701.
32. LaVela SL, Hill JN, Smith BM, et al. Healthcare worker influenza declination form program. Am J Infect Control. 2015;43:624–8.
33. Wicker S. Unvaccinated health care workers must wear masks during flu season-a possibility to improve influenza vaccination rates? Vaccine. 2009;27:2631–2.
34. Esposito S, Bonanni P, Maggi S, et al. Recommended immunization schedules for adults: Clinical practice guidelines by the Escmid Vaccine Study Group (EVASG), European Geriatric Medicine Society (EUGMS) and the World Association for Infectious Diseases and Immunological Disorders (WAidid). Hum Vaccin Immunother. 2016;12:1777–94.

Ongoing Threats for Older Europeans: Diphtheria, Pertussis and Tetanus

14

Giovanni Gabutti

Lifelong immunisation is key, since it promotes the prevention of infectious diseases across the whole lifetime, with the benefits of vaccination accessible at all ages. Vaccinating children and adolescents is an investment in the future, while productivity can be enhanced by vaccinating working-age adults. Vaccination over the life course, and particularly for older adults, makes it possible to maximise the contribution of older adults to society and to the economy and also helps to ensure the sustainability of healthcare systems by reducing the burden of vaccine-preventable diseases (VPDs).

There is strong political leadership on vaccination in Europe, and the life-course approach to vaccination is moving towards concrete actions at the level of the European Union (EU). At the level of the individual EU member countries, there is also good political intent, although concrete implementation varies on the ground. Italy is a good example of vaccination policy, with a lifetime immunisation schedule approved by several scientific societies. It includes all vaccines in every age class. This is a good example of how the issue of life-course vaccination could be approached.

The analysis of available epidemiological data, not only in Italy but also at the international level, has demonstrated the impact of the immunisation interventions adopted over the years. Irrespective of whether the desired levels of coverage are achieved, each vaccine intervention modifies the epidemiology of the various diseases with a reduction in morbidity and generally a lower spreading of the corresponding infectious agents. Booster vaccines are important in this regard, in particular when the duration of protection provided by the disease or immunisation is not long lasting, and the use of vaccination has made it possible to eliminate or reduce natural boosters. Thus, waning immunity can make successfully immunised

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_14

subjects become exposed to a new risk of acquiring the infection and/or the disease and transmitting it to others.

Our goals today in terms of vaccination are not only to consolidate the successes already achieved in the past but also to evaluate the consequences of the immunological pressure exerted by vaccination on the pathogens and to guarantee long-term protection.

Diphtheria, tetanus and pertussis are each examples of an ongoing health threat across the world. The question is does long-term immune protection exist for these diseases? Unfortunately, the answer is a resounding no, for all three diseases, where waning immunity is an important issue. Have we achieved a decrease of natural boosters? This question is not applicable for tetanus, because this agent is widespread everywhere, but for diphtheria and pertussis, the answer is definitely yes.

Besides, even if diphtheria has been eliminated, the reintroduction of the pathogen is still possible.

14.1 Tetanus

Tetanus is the only non-communicable VPD, so the concept of herd immunity is not applicable in this context. Data from the World Health Organization (WHO) estimate that the coverage rate with three doses of the combined diphtheria, tetanus and pertussis vaccine (DTP3) is around 86%. In 2011, it was estimated that there were over 70,000 deaths in children under 5 years of age, and in 2015 around 10,000 cases were reported. Tetanus occurs mainly in older patients, during the warmer months when outdoor activity is higher, and its current epidemiology in the EU may be explained by lack of vaccination or waning immunity. Tetanus notification in the EU is low, thanks to high coverage rates, and the number of cases is on the decline, with most occurring in the elderly. Despite the low number of cases, tetanus is severe with high mortality, and thus, maintaining high vaccination coverage is important. It also continues to pose a risk to unvaccinated people, so there is a need to implement catch-up and booster strategies, especially in areas where disease rates are highest.

14.2 Diphtheria

Diphtheria is a potentially acute disease caused by exotoxin-producing *Corynebacterium diphtheriae*. Morbidity and mortality result from the bacterial toxin that may cause obstructive pseudomembranes in the upper respiratory tract (croup) or damage to the myocardium and other tissues. Devastating diphtheria epidemics affecting mainly children have been described from many countries throughout history. 2015 global figures from the WHO reported 4530 cases, with an estimated DTP3 coverage of 86% and 28% of countries reaching >80% coverage in all districts.

Diphtheria is affected by waning immunity, although the majority of reported cases are in unvaccinated adults or those with unknown vaccination status. It is

therefore important to maintain high coverage rates. Diphtheria is a good example of how the epidemiology of a disease can be modified using vaccination. Seroprevalence in the pre-immunisation era was increasing with ageing as a consequence of natural infection and reached a plateau in adolescents and young adults due to natural boosters; in the post-immunisation era, seroprevalence is high after the completion of the vaccinal schedule in newborns but tends to decline, because of waning immunity and reduced natural boosters. The diphtheria vaccine effectively protects against the effects of the exotoxin produced by the pathogen, and immunisation is the only effective method of preventing the toxin-mediated disease. Since reported vaccine coverage is high in Europe, the probability of a widespread outbreak is low, but sporadic cases may continue to occur in unvaccinated or partially vaccinated individuals.

In terms of public health implications, enhanced diphtheria surveillance with high data completeness is warranted. Maintaining high vaccination coverage in the population is critical, and measures should be taken to improve vaccination coverage rates in under-vaccinated populations and certain risk groups (e.g. travellers planning to go to endemic areas and contacts of unvaccinated travellers returning from endemic areas, overcrowded closed groups of people under poor hygienic conditions, unvaccinated clusters and the elderly). Particular attention should also be given to revaccination of healthcare and social workers due to waning immunity, and revaccination of adult population against diphtheria every 10 years might be considered, as is currently the policy in some European countries.

14.3 Pertussis

Pertussis continues to represent a major cause of death in infants worldwide despite high vaccination coverage. Indeed, WHO figures reported 63,000 pertussis-related deaths in children aged <5 years in 2013 and over 140,000 cases across all age groups in 2015. Stratification of cases by age shows that it is not just a paediatric disease but primarily affects <1 year of age infants as well as children and adolescents up to 20 years of age. The clinical presentation of pertussis in adolescents and adults can be mild and often goes unrecognised. This poses an obvious risk of transmission to infants who are too young to have completed the primary pertussis vaccination series.

After a dramatic decline in the reported incidence of pertussis following the introduction of pertussis vaccines into national immunisation programmes some 50 years ago, reported pertussis incidence has increased markedly in recent years in almost all EU/EEA member states, as well as in other parts of the world. This increase has occurred despite sustained high vaccination coverage, highlighting the impact of waning vaccine immunity, while changes in circulating strains may also play a role. In addition, problems such as atypical forms, under-reporting, and under-diagnosis or missed diagnosis mean that figures are likely underestimated. Pertussis is the least well-controlled of all VPDs in Europe, and challenges remain to maintain high coverage and curb the resurgence of the disease. High vaccination

coverage must be maintained to ensure direct protection of infants and young children, the two groups which tend to show the most severe symptoms.

Outbreaks in areas of high vaccination coverage highlight that vaccination strategies may need to be revisited and that consideration should be given to adolescent and adult boosters. Some member states have already included some of these policies in their national immunisation schedule, with strategies that include vaccination of newborns, pre-school children, adolescents, adults, healthcare workers, child-care workers, pregnant woman or application of a cocoon strategy. An overall, integrated approach is required to ensure maximum efficacy.

In summary, the distinction between vaccination schedules for children, adolescents, adults and elderly is outdated, and we now need to think in terms of lifelong immunisation. Taking into account tetanus, diphtheria and pertussis, we must consolidate successes achieved heretofore and take into consideration the outcomes of the immunological pressure exerted on pathogens and the issue of waning immunity. Boosters make it possible to guarantee protection over time of already successfully immunised subjects who are exposed anew to the risk of acquiring and/or transmitting infections.

Herpes Zoster Vaccination: A Vaccine to Prevent Pain

15

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Is it desirable to prevent or attenuate herpes zoster, and if yes, is it possible by vaccination?

The varicella zoster virus (VZV) is an alpha herpesvirus that forms latency and can reactivate to cause a second infection. The alpha part of the name is important, as it places this virus in the same category as herpes simplex virus (HSV): both are neurotropic. The primary infection with VZV is varicella (chicken pox) and is usually, but not always, associated with full recovery. Reactivation occurs in the form of herpes zoster (HZ), commonly known as "shingles". In younger patients, shingles is often a painful rash that lasts 10–20 days and is usually followed by full recovery, albeit with the possibility of some hypo- or hyperpigmentation. However, in older and immunocompromised patients, post-herpetic neuralgia (PHN) is a common complication. Latency of the virus following primary infection occurs in sensory ganglia, but reactivation and neural transmission result in changes of neural architecture and function in the skin, the primary afferent nerve, and the sensory ganglion, where a large volume of normal neural tissue is replaced by scar tissue. In the spinal cord, the dorsal horn of the ipsilateral side can show atrophy.

VZV seropositivity, a marker of the presence of latent virus, is a prerequisite for the development of shingles. Most people become seropositive by the time they are adults, with more than 90% of children in temperate regions contracting chickenpox in the first 10–12 years of life [1]. Thus, the vast majority of people have the potential to develop shingles, and approximately one third of seropositive subjects do during their lifetime. The incidence of HZ increases with age, particularly beyond 60 and 70 years of age, with rates of approximately 3.2/1000 person-years overall and up to 10/1000 person-years above 80 years [2, 3]. The age-adjusted incidence of zoster has been shown to be increasing [4, 5].

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_15

Humans experience a natural decline in immunity with ageing, known as immunosenescence. This phenomenon affects both non-pathogen-specific innate immunity and pathogen-specific adaptive immunity [6]. Immunosenescence can affect both the number and function of immune cells, resulting in increased morbidity and mortality from infection and reduced vaccine responsiveness [7–9].

About 10% of shingles cases are not related to ageing but rather to immunosuppressive disease or immunosuppressant treatment. In an age-, sex-, calendar time-, and practice-matched case–control study from UK primary care, Hansson et al. estimated the association between 21 of the most common specific malignancies and subsequent zoster risk [10]. They found that malignancy overall was associated with an increased risk of zoster (adjusted odds ratio (OR) 1.29, 95% confidence interval (CI) 1.27–1.32), with haematological malignancies associated with an especially high risk [10]. However, the magnitude of the associations varied widely, and the strength of the association decreased as patient age increased.

Recurrent cases of HZ have been reported, with various studies suggesting recurrence rates ranging from 1 to 6% in immunocompetent individuals [11–13]. Recurrence is reported to be more frequent in women [12].

A frequent complication of HZ is post-herpetic neuralgia (PHN). It is difficult to ascertain the true rates of PHN incidence, since comparisons across studies are precluded by the lack of a standardized definition of PHN. Rates of PHN vary widely between studies [2, 3, 14–19], but it is clear that the older the patient, the longer the pain lasts after the zoster episode [20]. The current accepted definition of PHN is clinically significant pain (worst pain score ≥3 on a 0–10 scale where 10 represents worst imaginable pain) occurring or persisting at or beyond 90 days after HZ rash appearance. The main predictors for PHN are greater disease severity (pain and rash) and older age, while other factors such as female sex or immunosuppression have also been found to be associated with an increased risk [20, 21]. Prevalence of PHN for individuals aged ≥50 years is approximately 24% at 90 days after rash appearance and 11% at 180 days [22].

Other complications, although much less common, may nonetheless be serious and include neurological complications (other than PHN), such as an increased risk of stroke in the 6–12 months after HZ infections, encephalitis, cranial and motor neuron palsies or hearing loss. Ophthalmic complications, such as keratitis, uveitis or retinal necrosis leading to significant sight loss may sometimes accompany ophthalmic zoster. Cutaneous complications are seen, including bacterial superinfection or scarring. Visceral complications, which are very rare, may include myocarditis, pericarditis, arthritis or hepatitis.

The impact of HZ and PHN is far-reaching, affecting not only the patient but also the patient's family and caregivers, the healthcare economy and even employers via absenteeism or loss of productivity (presenteeism). Since retirement age is continually rising, more and more people with shingles will be among the working population, resulting in further loss of productivity. Functional ability declines with age, and HZ and PHN may accelerate this decline, and many patients will never regain the level of functioning appropriate for their age.

The MASTER study performed in Canada was a multicentre prospective cohort study of 261 HZ patients aged 50 years or over from 83 physician offices. The Zoster Brief Pain Inventory was used to measure severity of pain and interference with activities of daily living (ADL) because of pain, and the EuroQol EQ-5D assessment tool was used to measure quality of life [23]. The questionnaires were administered at regular intervals up to 180 days post-recruitment. Those patients who developed PHN, compared with those who did not, had significantly greater reduction in ADL from onset of HZ [23]. Overall, age-adjusted absenteeism- and presenteeism-related work loss was estimated at 31.6 h and 84.4 h, respectively, with a combined work loss of 116.0 h per HZ episode in a working person of 50–64 years of age [24]. This corresponds to about 3 weeks of lost work productivity for shingles, and it is also expensive in terms of healthcare expenditure. Indeed, in a study by Gialloreti et al., the direct costs of HZ (without PHN) were estimated at 122.68 ± 97.51 € for outpatient cases and more than 20 times higher (mean 2592 ± 1313 €) for patients requiring inpatient care [15]. Patients experiencing PHN incurred even higher costs, with an extra cost of 446 ± 442 € per episode of PHN in outpatients and 2806 ± 2641 € per PHN episode in inpatients. These data confirm the considerable financial burden resulting from HZ and PHN.

For the management of PHN, there exist a number of oral and topical therapies that have been shown to be superior to placebo for the treatment of PHN and neuropathic pain in general, but they have modest efficacy and often have a narrow therapeutic index. Indeed, most patients do not achieve adequate pain relief. In addition, in older patients with concomitant medication, adverse events are common. However, there is increasing evidence that sensory profiling using quantitative sensory testing (QST) may be able to predict response to treatment at the individual level in patients with neuropathic pain [25]. There is a lack of evidence supporting psychological or invasive therapies, including neuromodulation, in neuropathic pain.

There is clearly a rationale for vaccination against HZ. Available vaccines are the live attenuated VZV vaccine (Zostavax®) and the recently approved subunit adjuvanted vaccine (Shingrix®). Zostavax has been demonstrated to reduce incidence of HZ in immunocompetent adults ≥60 years by HZ by 51.3% ($P < 0.001$) and PHN by 66.5% ($P < 0.001$). It is more effective in younger than older subjects. At age 60–69 years, efficacy for HZ is 63.9 (90% CI 56–71) and above 70 years, 37.6 (90% CI 28–52). For PHN, efficacy is similar at all ages. Reactions at the injection site were more frequent among vaccine than placebo recipients but were generally mild [26]. Effectiveness studies have produced similar results.

Shingrix® is very effective, with overall vaccine efficacy against HZ of 97.2% (95% CI 93.7–99.0; $P < 0.001$), at age 60–69 years 97.4% (90.1–99.7, $P < 0.001$) and above 70 years 97.9% (87.9–100.0, $P < 0.001$) [27]. Without HZ one cannot develop PHN. Shingrix is significantly more reactogenic than Zostavax under study conditions. Nonetheless, 91% of patients with severe reaction returned for the second injection. Two doses of vaccine 2 months apart are required. There was no increased reactogenicity after the second injection. There was no evidence of increased immune-mediated diseases or exacerbation thereof [27]. Effectiveness

studies are not available as the vaccine has only recently been licensed. It is likely that Shingrix will be suitable for protection of immunocompromised subjects.

Overall, with our current state of knowledge, we can confidently say that HZ is worth preventing. In answer to the question as to whether it is possible to prevent it through vaccination, the answer is yes for those whom the vaccine is available. Some at-risk populations may not have this advantage, thus underlining the compelling need to pursue research on possible drugs effective in managing HZ and its complications.

References

1. Sengupta N, Booy R, Schmitt HJ, Peltola H, Van-Damme P, Schumacher RF, et al. Varicella vaccination in Europe: are we ready for a universal childhood programme? Eur J Pediatr. 2008;167(1):47–55.
2. Gauthier A, Breuer J, Carrington D, Martin M, Remy V. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. Epidemiol Infect. 2009;137(1):38–47.
3. Stein AN, Britt H, Harrison C, Conway EL, Cunningham A, Macintyre CR. Herpes zoster burden of illness and health care resource utilisation in the Australian population aged 50 years and older. Vaccine. 2009;27(4):520–9.
4. Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc. 2007;82(11):1341–9.
5. Lu PJ, Euler GL, Harpaz R. Herpes zoster vaccination among adults aged 60 years and older, in the U.S., 2008. Am J Prev Med. 2011;40(2):e1–6.
6. Aspinall R, Del Giudice G, Effros RB, Grubeck-Loebenstein B, Sambhara S. Challenges for vaccination in the elderly. Immun Ageing. 2007;4:9.
7. Caruso C, Buffa S, Candore G, Colonna-Romano G, Dunn-Walters D, Kipling D, et al. Mechanisms of immunosenescence. Immun Ageing. 2009;6:10.
8. Kumar R, Burns EA. Age-related decline in immunity: implications for vaccine responsiveness. Expert Rev Vaccines. 2008;7(4):467–79.
9. Boraschi D, Del Giudice G, Dutel C, Ivanoff B, Rappuoli R, Grubeck-Loebenstein B. Ageing and immunity: addressing immune senescence to ensure healthy ageing. Vaccine. 2010;28(21):3627–31.
10. Hansson E, Forbes HJ, Langan SM, Smeeth L, Bhaskaran K. Herpes zoster risk after 21 specific cancers: population-based case-control study. Br J Cancer. 2017;116(12):1643–51.
11. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. BMJ Open. 2014;4(6):e004833.
12. Shiraki K, Toyama N, Daikoku T, Yajima M, Miyazaki Dermatologist S. Herpes zoster and recurrent herpes zoster. Open Forum Infect Dis. 2017;4(1):ofx007.
13. Yawn BP, Wollan PC, Kurland MJ, St Sauver JL, Saddier P. Herpes zoster recurrences more frequent than previously reported. Mayo Clin Proc. 2011;86(2):88–93.
14. Helgason S, Petursson G, Gudmundsson S, Sigurdsson JA. Prevalence of postherpetic neuralgia after a first episode of herpes zoster: prospective study with long term follow up. BMJ. 2000;321(7264):794–6.
15. Gialloreti LE, Merito M, Pezzotti P, Naldi L, Gatti A, Beillat M, et al. Epidemiology and economic burden of herpes zoster and post-herpetic neuralgia in Italy: a retrospective, population-based study. BMC Infect Dis. 2010;10:230.
16. Opstelten W, Mauritz JW, de Wit NJ, van Wijck AJ, Stalman WA, van Essen GA. Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database. Fam Pract. 2002;19(5):471–5.

17. Ultsch B, Koster I, Reinhold T, Siedler A, Krause G, Icks A, et al. Epidemiology and cost of herpes zoster and postherpetic neuralgia in Germany. Eur J Health Econ. 2013;14(6):1015–26.
18. Weitzman D, Shavit O, Stein M, Cohen R, Chodick G, Shalev V. A population based study of the epidemiology of Herpes Zoster and its complications. J Infect. 2013;67(5):463–9.
19. Yawn BP, Gilden D. The global epidemiology of herpes zoster. Neurology. 2013;81(10):928–30.
20. Meister W, Neiss A, Gross G, Doerr HW, Hobel W, Malin JP, et al. A prognostic score for postherpetic neuralgia in ambulatory patients. Infection. 1998;26(6):359–63.
21. Forbes HJ, Bhaskaran K, Thomas SL, Smeeth L, Clayton T, Mansfield K, et al. Quantification of risk factors for postherpetic neuralgia in herpes zoster patients: a cohort study. Neurology. 2016;87(1):94–102.
22. Drolet M, Brisson M, Schmader K, Levin M, Johnson R, Oxman M, et al. Predictors of postherpetic neuralgia among patients with herpes zoster: a prospective study. J Pain. 2010;11(11):1211–21.
23. Drolet M, Brisson M, Schmader KE, Levin MJ, Johnson R, Oxman MN, et al. The impact of herpes zoster and postherpetic neuralgia on health-related quality of life: a prospective study. CMAJ. 2010;182(16):1731–6.
24. Singhal PK, Makin C, Pellissier J, Sy L, White R, Saddier P. Work and productivity loss related to herpes zoster. J Med Econ. 2011;14(5):639–45.
25. Holbech JV, Bach FW, Finnerup NB, Jensen TS, Sindrup SH. Pain phenotype as a predictor for drug response in painful polyneuropathy-a retrospective analysis of data from controlled clinical trials. Pain. 2016;157(6):1305–13.
26. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med. 2005;352(22):2271–84.
27. Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang SJ, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med. 2015;372(22):2087–96.

Gastroenteritis Burden in the Adult Community: Prospects for Vaccines

16

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The Global Burden of Diseases collaborators reported in 2016 that among the 30 leading causes of death over the last decade, diarrhoeal disease (GE) is the ninth cause of death overall worldwide. However, from 2005 to 2015, there was a decrease in the overall death rate from GE, due to a substantial decrease in age-specific mortality rates that was not totally offset by the increases due to population growth and population ageing over the same period [1].

One may wonder which countries or population groups bear the burden of GE. In fact, the specific causes of GE in adults and the elderly are poorly identified. In a study performed by Lopman et al. among all gastroenteritis-associated hospital discharges during 1996–2007 from a nationally representative data set of hospital inpatient stays in the USA, the cause of GE was unspecified at discharge in 69% of cases [2]. Severe GE leading to hospitalization and death is more frequently observed in the elderly, and in the last decade, US surveillance has highlighted an increase in hospitalizations among elders [2].

Diarrhoeal disease represents a major disease burden, particularly among children under 5 years of age, in whom peak GE incidence is observed, and among elderly adults, in whom severe GE leading to hospitalization and resulting in death is most frequently observed [2–4].

Age is thus clearly a very important risk factor. Indeed, a surveillance study of over 90,000 hospitalizations with GE as the discharge diagnosis showed a tenfold higher case fatality in older as compared to younger patients, with age found to be the most important risk factor for death subsequent to a hospitalization involving GE (odds ratio (OR) 52.6, 95% confidence interval (CI) 37.0–76.9 for age ≥70 years vs. <5 years) [5]. These results have been confirmed in other countries around the world. In a prospective longitudinal cohort study of Australian adults aged ≥45 years (mean 62.7 years) at recruitment in 2006–2009, Chen et al. report a crude incidence

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_16

of hospitalizations due to GE of 5.5 per 1000 person-years (95% CI 5.3–5.6), which differed by age, sex, household income and region of residence [6]. Incidence rose ninefold from 2.4 hospitalizations per 1000 (95% CI 2.2–2.5) person-years in individuals aged 45–54 years to 21.8 per 1000 (95% CI 20.2–23.6) in those aged 85 years and older ($p < 0.001$ for linear trend). The rate of hospitalizations due to gastroenteritis was higher in women than in men, but for both sexes, hospitalization rates increased with decreasing household income ($p < 0.001$) [6]. Both the length of stay and the proportion with complications increased with increasing age. Among cases, 2.6% (160/6077) of the patients died within 30 days of hospital admission, with patients aged ≥65 years accounting for the majority of these deaths (90.6%, $n = 145$) [6]. Finally, Chen et al. also reported significant associations between GE and poorer self-reported health, the use of proton-pump inhibitors, underweight and obesity, and female sex (possibly due to inadequate family care for older women). Conversely, no significant associations were observed with food consumption [6].

16.1 Which Aetiologic Agents Are Responsible for GE?

The aetiology of transmission modes as reported by the US surveillance systems shows that around 60% are person-to-person environmental transmissions and only about 30% are food- and water-borne [7]. Among 7430 outbreaks with a suspected or confirmed aetiology reported, norovirus was predominant, reported in 84% overall, and was the only suspected or confirmed aetiology in 62% ($n = 5720/9193$) outbreaks transmitted through person-to-person contact. The most common settings reported were long-term care facilities (70%), schools (8%), child care facilities (7%) and hospitals (4%) [7]. Outbreaks suspected or confirmed to be caused by norovirus or an unknown aetiology most often occurred in long-term care facilities (78% and 71% of outbreaks, respectively), while shigella, salmonella and outbreaks of other aetiologies were most often observed in child care facilities. Among 5405 outbreaks with information on age distribution of cases, 12% of cases occurred in children aged <10 years, 21% in adolescents and adults aged 10–49 years and 49% of cases in adults aged >49 years [7]. It is estimated that norovirus plays an important role in the economic burden of GE diseases, and although the total economic burden is greatest in young children, the highest cost per illness is observed among older age groups, largely due to productivity losses resulting from acute illness [8]. Older adults in the European region had the highest health system cost per illness, whereas older adults in the Americas had the highest societal illness costs due to lost productivity [8].

The aetiology of GE outbreaks in long-term care facilities shows that norovirus and rotavirus together account for 96% of all infections [9]. However, a recent Danish study among 265 adults admitted to hospital with acute GE showed that in a large proportion (62.3%) of patients, no pathogen was found [10], while 9.4% tested positive for rotavirus and enteropathogenic bacteria were found in 24.5% of cases. In this study, risk factors thought to play a role were not found to predict rotavirus GE, such as close contact with children or travel activity, and the seasonality of rotavirus

differed markedly from that of bacterial GE [10]. Overall, rotavirus was the second-most frequent pathogen, exceeded only by *Campylobacter* spp. [10].

The introduction of rotavirus vaccination in infants in the USA in 2006 led to a dramatic decline in the number of infections, and although adults are not the target population for this vaccine, there is evidence of indirect protection through infant vaccination [11, 12]. As a result, the World Health Organization recommended in 2009 that rotavirus vaccines be included in all national immunization programmes.

In the hospital setting, *Clostridium difficile* is a common cause of antibiotic-associated diarrhoea, and infection may lead to sepsis or even death. The majority of infections with *C. difficile* occur among persons aged over 65 years and in those in healthcare facilities, such as hospitals and long-term care facilities. From 1996 to 2009, *C. difficile* rates for hospitalized persons aged ≥65 years increased 200%, with increases of 175% for those aged 65–74 years, 198% for those aged 75–84 years and 201% for those aged ≥85 years. Rates of infection were notably higher among those aged ≥85 years than in other age groups [13]. There is a high rate of asymptomatic carriage, with 4–10% of long-term care residents colonized, and during outbreaks, more than 50% of residents with no symptoms have positive stools [14–22].

However, data are sparse regarding this pathogen in European hospitals, and thus, the true extent of *Clostridium* infection is likely underestimated, due to inadequate laboratory diagnosis, absence of clinical suspicion and wide variation in testing frequency and diagnostic methods [23]. A study performed over a 5-year period in a teaching hospital in Liguria, the Italian region with the oldest population, showed increase in incidence and testing over the study period. The incidence of *Clostridium difficile* infection may have been overestimated due to the increase in the number of patients tested over the years, but the simultaneous increase in the proportion of test-positive patients seems to confirm the role of *C. difficile* as an increasing cause of healthcare-associated diarrhoea [24].

Clearly norovirus, rotavirus and *Clostridium* are common agents in different settings and cause a major burden of disease, particularly among the elderly, subjects in long-term care facilities, hospitalized patients and children under 5 years of age. However, they have different epidemiological pictures in different settings with varying burdens, thus requiring different vaccination strategies. It must be remembered that vaccination programmes need to take into account the fact that some groups have higher risk of infection and clinical complications (elderly, nursing home residents, travellers), while others have higher risk of transmitting infection to other groups (healthcare workers, food handlers), and some can have both (young children, immunocompromised patients). Vaccine development is at different stages for these various infectious agents. Norovaccines are currently under development [25, 26], and potential target populations include high-risk individuals susceptible to infection (e.g. young children, the elderly, nursing home residents, travellers, immunocompromised individuals), as well as transmitters of the virus (e.g. young children, food handlers, healthcare workers).

Rotavirus vaccination has a longer history. The first vaccine was licensed in the USA 20 years ago but was subsequently withdrawn from the market because of an

increased risk of intussusception. Currently, two vaccines are licensed and used worldwide with demonstrated effectiveness [27, 28]. Finally, regarding *Clostridium*, intense research in recent years has led to development of experimental vaccines that are at various stages of development [29]. One formalin-inactivated toxoid-based vaccine has reached phase III development, with an ongoing trial to assess the safety and efficacy in patients at risk aged 50 years and over [30].

In conclusion, GE is associated with a substantial burden of disease, incurring high direct and indirect costs for healthcare and lost productivity. Passive surveillance is poorly effective, and the aetiology of GE is poorly defined. Age is the most important risk factor for hospitalization and death. GE hospitalizations are rising in subjects aged >65 years, and GE in adults imposes major burden on patient and healthcare system, with a particularly heavy impact in long-term care facilities and hospitals. The main pathogens are norovirus, rotavirus and *Clostridium difficile*. Vaccines, old and new, are at different phases of preclinical and clinical development. Vaccination strategies should be put in place, but the target populations remain to be defined. The potential population-level effects and the cost-effectiveness of vaccination also warrant further investigation. Finally, bridging the gap between developed and developing world markets is an important point from an ethical point of view.

References

1. Mortality GBD, Causes of Death C. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1459–544.
2. Lopman BA, Hall AJ, Curns AT, Parashar UD. Increasing rates of gastroenteritis hospital discharges in US adults and the contribution of norovirus, 1996–2007. Clin Infect Dis. 2011;52(4):466–74.
3. Kirk MD, Hall GV, Becker N. Gastroenteritis in older people living in the community: results of two Australian surveys. Epidemiol Infect. 2012;140(11):2028–36.
4. Kirk MD, Pires SM, Black RE, Caipo M, Crump JA, Devleesschauwer B, et al. World Health Organization estimates of the global and regional disease burden of 22 foodborne bacterial, protozoal, and viral diseases, 2010: a data synthesis. PLoS Med. 2015;12(12):e1001921.
5. Gangarosa RE, Glass RI, Lew JF, Boring JR. Hospitalizations involving gastroenteritis in the United States, 1985: the special burden of the disease among the elderly. Am J Epidemiol. 1992;135(3):281–90.
6. Chen Y, Liu BC, Glass K, Kirk MD. High incidence of hospitalisation due to infectious gastroenteritis in older people associated with poor self-rated health. BMJ Open. 2015;5(12):e010161.
7. Wikswo ME, Kambhampati A, Shioda K, Walsh KA, Bowen A, Hall AJ, et al. Outbreaks of acute gastroenteritis transmitted by person-to-person contact, environmental contamination, and unknown modes of transmission—United States, 2009–2013. MMWR Surveill Summ. 2015;64(12):1–16.
8. Bartsch SM, Lopman BA, Ozawa S, Hall AJ, Lee BY. Global economic burden of norovirus gastroenteritis. PLoS One. 2016;11(4):e0151219.
9. Barret AS, Jourdan-da Silva N, Ambert-Balay K, Delmas G, Bone A, Thiolet JM, et al. Surveillance for outbreaks of gastroenteritis in elderly long-term care facilities in France, November 2010 to May 2012. Euro Surveill. 2014;19(29):20859.

10. Lausch KR, Westh L, Kristensen LH, Lindberg J, Tarp B, Larsen CS. Rotavirus is frequent among adults hospitalised for acute gastroenteritis. Dan Med J. 2017;64(1):A5312.
11. Anderson EJ, Shippee DB, Weinrobe MH, Davila MD, Katz BZ, Reddy S, et al. Indirect protection of adults from rotavirus by pediatric rotavirus vaccination. Clin Infect Dis. 2013;56(6):755–60.
12. Lopman BA, Curns AT, Yen C, Parashar UD. Infant rotavirus vaccination may provide indirect protection to older children and adults in the United States. J Infect Dis. 2011;204(7):980–6.
13. National Center for Health Statistics. Rates of *Clostridium difficile* infection among hospitalized patients aged ≥65 years,* by Age Group—National Hospital Discharge Survey, United States, 1996–2009. MMWR Morb Mortal Wkly Rep. 2011;60(34):1171.
14. Riggs MM, Sethi AK, Zabarsky TF, Eckstein EC, Jump RL, Donskey CJ. Asymptomatic carriers are a potential source for transmission of epidemic and nonepidemic *Clostridium difficile* strains among long-term care facility residents. Clin Infect Dis. 2007;45(8):992–8.
15. Arvand M, Moser V, Schwehn C, Bettge-Weller G, Hensgens MP, Kuijper EJ. High prevalence of *Clostridium difficile* colonization among nursing home residents in Hesse, Germany. PLoS One. 2012;7(1):e30183.
16. Campbell RR, Beere D, Wilcock GK, Brown EM. *Clostridium difficile* in acute and long-stay elderly patients. Age Ageing. 1988;17(5):333–6.
17. Rudensky B, Rosner S, Sonnenblick M, van Dijk Y, Shapira E, Isaacsohn M. The prevalence and nosocomial acquisition of *Clostridium difficile* in elderly hospitalized patients. Postgrad Med J. 1993;69(807):45–7.
18. Walker KJ, Gilliland SS, Vance-Bryan K, Moody JA, Larsson AJ, Rotschafer JC, et al. *Clostridium difficile* colonization in residents of long-term care facilities: prevalence and risk factors. J Am Geriatr Soc. 1993;41(9):940–6.
19. Rivera EV, Woods S. Prevalence of asymptomatic *Clostridium difficile* colonization in a nursing home population: a cross-sectional study. J Gend Specif Med. 2003;6(2):27–30.
20. Ryan J, Murphy C, Twomey C, Paul Ross R, Rea MC, MacSharry J, et al. Asymptomatic carriage of *Clostridium difficile* in an Irish continuing care institution for the elderly: prevalence and characteristics. Ir J Med Sci. 2010;179(2):245–50.
21. Fulton JD, Fallon RJ. Is *Clostridium difficile* endemic in chronic-care facilities? Lancet. 1987;2(8555):393–4.
22. Simor AE, Yake SL, Tsimidis K. Infection due to *Clostridium difficile* among elderly residents of a long-term-care facility. Clin Infect Dis. 1993;17(4):672–8.
23. Davies KA, Longshaw CM, Davis GL, Bouza E, Barbut F, Barna Z, et al. Underdiagnosis of *Clostridium difficile* across Europe: the European, multicentre, prospective, biannual, point-prevalence study of *Clostridium difficile* infection in hospitalised patients with diarrhoea (EUCLID). Lancet Infect Dis. 2014;14(12):1208–19.
24. Alicino C, Giacobbe DR, Durando P, Bellina D, DI Bella AM, Paganino C, et al. Increasing incidence of *Clostridium difficile* infections: results from a 5-year retrospective study in a large teaching hospital in the Italian region with the oldest population. Epidemiol Infect. 2016;144(12):2517–26.
25. Debbink K, Lindesmith LC, Baric RS. The state of norovirus vaccines. Clin Infect Dis. 2014;58(12):1746–52.
26. Tan M, Jiang X. Vaccine against norovirus. Hum Vaccin Immunother. 2014;10(6):1449–56.
27. Yen C, Tate JE, Hyde TB, Cortese MM, Lopman BA, Jiang B, et al. Rotavirus vaccines: current status and future considerations. Hum Vaccin Immunother. 2014;10(6):1436–48.
28. Soares-Weiser K, Maclehose H, Bergman H, Ben-Aharon I, Nagpal S, Goldberg E, et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database Syst Rev. 2012;11:CD008521.
29. Leuzzi R, Adamo R, Scarselli M. Vaccines against *Clostridium difficile*. Hum Vaccin Immunother. 2014;10(6):1466–77.
30. de Bruyn G, Saleh J, Workman D, Pollak R, Elinoff V, Fraser NJ, et al. Defining the optimal formulation and schedule of a candidate toxoid vaccine against *Clostridium difficile* infection: a randomized phase 2 clinical trial. Vaccine. 2016;34(19):2170–8.

Travel Vaccination

17

Andrea Rossanese

17.1 Background

The World Tourism Organization estimated the number of international tourist arrivals to be 1.2 billion in 2016, an increase of 46 million over the previous year, a figure that has been rising constantly for 7 consecutive years [1]. In this context, a long list of vaccines are dispensed and administered in travel clinics around the world, and there are currently around 250 under development.

There are two main steps in immunizing travelers, namely, to update routine vaccinations and, second, to provide travel-specific immunization.

For the first step, knowledge of a patient's previous immunizations is necessary, and the patient's personal medical history also needs to be taken into account.

For the second step, there are considerably more issues to be covered. Detailed information must be obtained about the patient's itinerary, their planned living conditions during the journey, the mode of travel (e.g., adventure travel or chaperoned luxury tour), and the purpose of travel (e.g., medical or veterinary work, tourism, business, visiting relatives/friends). Although sometimes mistakenly regarded as a rote selection of vaccines based on destination country, the choice of vaccines more often requires thoughtful consideration based on details of the patient's medical history, knowledge of vaccine interactions with other vaccines or medications, timing of departure and nature of travel with regard to risk for vaccine-preventable diseases, and patient preferences. Indeed, cost is a growing factor in a traveler's decision-making process about which vaccines to receive. Travelers with limited means and incomplete insurance coverage may be forced to make decisions about which family members to protect (often choosing children, leaving adults vulnerable) or may choose, because of cost, to limit vaccines to those such as yellow fever vaccine, because it is legally required for entry into some countries.

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_17

We will focus here on three major and common travel vaccines, namely, yellow fever, dengue, and rabies.

17.2 Yellow Fever

Yellow fever (YF) is caused by the yellow fever virus (YFV), which is a member of the *Flavivirus* genus. The disease manifests as a viral hemorrhagic fever, with typically abrupt onset and flu-like symptoms, such as fever, muscle pain (particularly backache), headache, shivering, loss of appetite, and nausea or vomiting. Clinical symptoms of disease range from asymptomatic infection to death. It is endemic to tropical and subtropical regions of Central and South America and sub-Saharan Africa and is transmitted to humans via the bites of *Haemagogus* and *Aedes* mosquitoes [2]. Estimates indicate that there are up to 200,000 cases of YF annually, with 30,000 to 60,000 deaths per year [3]. There has been a resurgence of the disease in both Africa and South America, affecting both locals and travelers.

The YF vaccine is a highly potent, live-attenuated vaccine, and a special permit is required in several countries to store and administer the vaccine, as is the case in Italy, for example, as well as in most other European Union (EU) countries. Centers that are certified to give YF vaccines must be declared to the national health authorities.

YF vaccine may be required to travel to a specific country under the 2005 International Health Regulations [4] or may be simply recommended because of the risk of contracting YF during travel to an endemic area. The certificate of vaccination becomes valid 10 days after administration of the vaccine, and, since July 2016, the 10-year booster requirement has been eliminated, and the vaccine is now valid for the lifetime. This is a retroactive measure, meaning that any International Certificate of Vaccination or Prophylaxis (ICVP), even those dating from more than 10 years ago, is now still valid. This measure was introduced further to the publication of updated studies and a position paper by WHO stating that a single dose of YF vaccine is sufficient to confer sustained lifelong protective immunity against YF disease and that a booster dose is not necessary [5, 6]. This decision was in line with the 2015 advisory from the Centers for Disease Control and Prevention (CDC) [7]. However, in view of the paucity of data in certain contexts, the CDC subsequently published a report stating that certain categories of individuals still require a booster dose, namely, women who were pregnant at first administration (regardless of the trimester of pregnancy), recipients of hematopoietic stem cell transplant after yellow fever vaccination who are sufficiently immunocompetent to be safely vaccinated, laboratory workers working with wild YFV, patients who were HIV positive when they received their last dose, and those who had a first dose 10 years or more previously and who will be traveling in a higher-risk context based on season, location, activities, and duration of their travel [8].

In this context, there remains some uncertainty regarding the lifelong protection of YF vaccination for travelers, and, indeed, there is insufficient evidence to count on lifelong protection after a single dose, especially for travelers from non-endemic

areas. Indeed, Niedrig et al. reported, among 209 subjects receiving YFV between <1 and up to 38 years previously, that there was a significant decline in the percentage of reactive sera (with an NT titer >1:10) from 94% positive results in the first year after vaccination to 74.5% after 10 years [9]. Furthermore, in many published studies, the majority of those vaccinated lived or stayed for prolonged periods of time; thus, there was a possible role of natural immunity and/or natural "boosters." Finally, the methods of measuring immune response after YFV varied between studies, with Niedrig et al. reporting that no correlation was observed between results obtained with neutralization test (NT), immunofluorescence test (IFT), hemagglutination inhibition test (HIT), and ELISA for YF-specific IgG antibodies [9].

YF vaccination can be associated with adverse events, with mild events such as headache, myalgia, low-grade fever, discomfort at the injection site, pruritus, urticaria, and rash being reported by up to 25% of vaccine recipients, and substantially higher rates of serious adverse events occurring in persons aged 60 years and older [10]. Among the serious adverse events that may present after YF vaccine, YF vaccine-associated neurotropic disease (YF-AND) constitutes a group of neurologic conditions caused by direct viral invasion of the central nervous system by the vaccine virus or an autoimmune reaction [6]. The reported rate of YF-AND is 0.25–0.8 per 100,000 vaccine doses in primary vaccines, but this rate rises to 1.6 in persons aged 60–69 and 2.3 in those aged 70 years and over [10]. A second type of serious adverse event after YF vaccine is YF vaccine-associated viscerotropic disease (YF-AVD), caused by replication and dissemination of the vaccine virus in a manner similar to the natural virus [6]. YF-AVD also has higher reporting rates among older persons, with practically no cases occurring in those aged under 60, but 1 per 100,000 doses among those aged 60 to 69 and 2.3 per 100,000 doses in those aged 70 years and over [10]. Both YF-AND and YF-AVD are extremely rare and rarely, if ever, observed after a booster dose. In the context of outbreak control, it was shown by Ahuka-Mundeke et al. that a fractional dose (containing one fifth of the standard dose) was effective in inducing seroconversion in 98% (95% CI 96–99) of individuals who were seronegative at baseline [11]. This finding is highly relevant, since it shows that a reduced dose may be useful in controlling an outbreak of YF when supplies of the vaccine are constrained. However, fractional doses of YF vaccine are not generally recommended for travelers, because data regarding the duration of efficacy and safety are still inadequate, and an ICVP for YF cannot be issued after administration of a fractional dose.

17.3 Rabies

Rabies is an underreported and neglected tropical zoonotic disease with a case fatality rate of almost 100% [12]. It is estimated that globally, canine rabies causes approximately 59,000 (95% CI, 25–159,000) deaths and over 3.7 million (95% CI, 1.6–10.4 million) disability-adjusted life years (DALYs) annually [13]. Since death from rabies can be prevented by appropriate prophylaxis, no vaccinated individuals die [14]. The WHO and its partners have set a goal of zero human deaths from

dog-transmitted rabies by 2030 [15]. To induce long-lasting immunologic memory, the WHO approved tissue culture rabies preexposure vaccine at 0, 7, and 21–28 days. However, this vaccine schedule is extremely costly and may be prohibitive for many of those who need it. It is cumbersome to implement, as it involves three visits to the clinic/hospital, and, finally, there are often vaccine shortages. In this context, a recent study showed that a single dose, with a single booster 1 year later, was sufficient to mount an adequate anamnestic antibody response [16]. Similarly, a recent non-inferiority trial in 500 healthy adults compared the safety and immunogenicity of a two-visit (day 0 and day 7) intradermal vaccine, with a single booster dose given 1–3 years later [12]. The authors reported that all subjects had seroconversion 7 days after the booster dose, while any injection site reactions were mild and transient [12]. The authors thus conclude that in healthy adults, a double dose over two visits at day 0 and day 7 is at least as effective as the standard three-dose schedule. The WHO recently issued a new position paper on rabies vaccination with new recommendations based on the latest evidence [17] and recommends two main immunization strategies for the prevention of human rabies, namely, postexposure prophylaxis (including thorough wound washing at the exposure site, plus administration of rabies immunoglobulin if indicated, as well as administration of a course of several doses of rabies vaccine) and preexposure prophylaxis, comprising the administration of several doses of rabies vaccine before exposure for individuals at high risk. Individual assessment of risk is recommended for travelers, including considerations such as the remoteness of their destination in endemic areas, where rapid access to prophylaxis may not be guaranteed in case of exposure, the prevailing rabies epidemiology, and the duration of stay [17].

17.4 Dengue

Dengue is a viral infection mainly acquired through the bites of infected *Aedes aegypti* mosquitoes. Travelers are at highest risk in urban areas in most tropical countries. Symptoms range from a mild, flu-like illness to high fever and rash associated with severe headache and muscle, joint, and back pain. Classic dengue is self-limited (average duration 6 days), but severe fatigue that lasts for weeks or months may ensue. Rarely, severe cases progress to significant hemorrhage and organ damage. The keystone of prevention is based on personal protective measures against mosquito bites. Approximately 3.9 billion people are estimated to be at risk in 128 countries, and there are almost 400 million infections per year, of which 100 million are clinically manifest [18].

Developing an effective vaccine against dengue has proven to be challenging. Indeed, there are four distinct dengue serotypes, and cross-reactive immunity has been suspected to result in more severe disease among individuals who were dengue-naïve at the time of immunization [19, 20]. This led the Philippines to discontinue dengue vaccination in 2017, because it was considered dangerous [21]. Recent data conclusively indicate that persons receiving the tetravalent dengue

vaccine who had not been infected with dengue virus prior to vaccination had a higher risk of more severe illness and hospitalization due to dengue compared with unvaccinated persons [22]. The WHO now recommends that this specific vaccine only be administered to persons with proven dengue infection prior to vaccination, which effectively precludes most travelers as well as endemic individuals who have no access to testing for dengue antibodies. The tetravalent dengue vaccine is approved in approximately 20 dengue-endemic countries, but travelers and expatriates are advised to avoid it unless they have reliable laboratory evidence of past dengue infection. A new candidate vaccine currently under development may be more suitable for dengue-naive individuals and has shown promising safety results, but is not commercially approved at this time [23].

17.5 Conclusion

For traveler vaccines, it is essential to reflect seriously on disease-related risk (high risk of infection but low impact, e.g., diarrhea, or low risk/high impact, e.g., rabies, yellow fever). It should be remembered that vaccines exist both to protect the visited populations and the travelers, plus those the travelers come in contact with on their return from endemic areas. In addition, travel should be used as a good opportunity to update routine vaccines. An additional issue that merit consideration is priming of immunological memory with a single dose, according to the principle that every dose counts in protecting against vaccine-preventable diseases. When considering the need for travel vaccines, it is also important to relate the timing of vaccination to the period of exposure (e.g., for rabies, considering the high risk and short period of exposure, any dose of vaccine is better than none).

Rapid advances in biotechnology promise a potential revolution in the development of new vaccines using diverse approaches ranging from DNA vaccines to transgenic plant vaccines, although significant technical hurdles remain. New candidate vaccines show promise in protecting against diverse pathogens that cause diarrheal disease. Optimism remains for the eventual development of vaccines against dengue fever, HIV, and malaria. In addition to the remaining technical hurdles, however, equally formidable economic hurdles remain in adequate funding of vaccine research and development against diseases that mostly afflict the poorest populations in the poorest countries. The increased interest in travel and travel immunizations by more affluent travelers may provide substantial assistance in making these much needed vaccines a reality.

References

1. World Tourism Organization (UNWTO). UNWTO Annual Report 2016. UNWTO, Madrid, Spain. 2017. https://www.e-unwto.org/doi/pdf/10.18111/9789284418725. Accessed 29 June 2018.
2. Douam F, Ploss A. Yellow fever virus: knowledge gaps impeding the fight against an old foe. Trends Microbiol. 2018;26(11):913–28.

3. World Health Organization. WHO global yellow fever data base. http://apps.who.int/globalatlas/default.asp. Accessed 30 June 2018. (Latest data for Yellow Fever from 2005).
4. World Health Organization. International Health Regulations. 3rd ed. 2005. http://www.who.int/ihr/publications/9789241580496/en/. Accessed 30 June 2018.
5. Meeting of the Strategic Advisory Group of Experts on immunization, April 2013—conclusions and recommendations. Wkly Epidemiol Rec. 2013;88(20):201–6.
6. Vaccines and vaccination against yellow fever. WHO position paper—June 2013. Wkly Epidemiol Rec. 2013;88(27):269–83.
7. Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices (ACIP): summary report, February 26, 2015. Atlanta, GA: US Department of Health and Human Services, CDC; 2015. http://www.cdc.gov/vaccines/acip/meetings/meetings-info.html. Accessed 30 June 2018.
8. Staples JE, Bocchini JA Jr, Rubin L, Fischer M, Centers for Disease C, Prevention. Yellow fever vaccine booster doses: recommendations of the Advisory Committee on Immunization Practices, 2015. MMWR Morb Mortal Wkly Rep. 2015;64(23):647–50.
9. Niedrig M, Lademann M, Emmerich P, Lafrenz M. Assessment of IgG antibodies against yellow fever virus after vaccination with 17D by different assays: neutralization test, haemagglutination inhibition test, immunofluorescence assay and ELISA. Tropical Med Int Health. 1999;4(12):867–71.
10. Lindsey NP, Schroeder BA, Miller ER, Braun MM, Hinckley AF, Marano N, et al. Adverse event reports following yellow fever vaccination. Vaccine. 2008;26(48):6077–82.
11. Ahuka-Mundeke S, Casey RM, Harris JB, Dixon MG, Nsele PM, Kizito GM, et al. Immunogenicity of fractional-dose vaccine during a yellow fever outbreak—preliminary report. N Engl J Med. 2018. https://doi.org/10.1056/NEJMoa1710430
12. Soentjens P, Andries P, Aerssens A, Tsoumanis A, Ravinetto R, Heuninckx W, et al. Pre-exposure intradermal rabies vaccination: a non-inferiority trial in healthy adults on shortening the vaccination schedule from 28 to 7 days. Clin Infect Dis. 2018. https://doi.org/10.1093/cid/ciy513
13. Hampson K, Coudeville L, Lembo T, Sambo M, Kieffer A, Attlan M, et al. Estimating the global burden of endemic canine rabies. PLoS Negl Trop Dis. 2015;9(4):e0003709.
14. Dodet B, Durrheim DN, Rees H. Rabies: underused vaccines, unnecessary deaths. Vaccine. 2014;32(18):2017–9.
15. World Health Organization. Zero by 30: the global strategic plan to prevent human deaths from dog-transmitted rabies by 2030. 2017. http://www.who.int/rabies/Executive_summary_draft_V3_wlogo.pdf?ua=1. Accessed 1 July 2018.
16. Jonker EFF, Visser LG. Single visit rabies pre-exposure priming induces a robust anamnestic antibody response after simulated post-exposure vaccination: results of a dose-finding study. J Travel Med. 2017;24(5).
17. World Health Organization. Rabies vaccines: WHO position paper—April 2018. Weekly Epidemiological Record No. 16, 2018, 93, 201–20. Weekly Epidemiological Record 2018;93(16):201–20. http://www.who.int/rabies/resources/who_wer9316/en/. Accessed 1 July 2018.
18. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013;496(7446):504–7.
19. Anderson KB, Endy TP, Thomas SJ. The dynamic role of dengue cross-reactive immunity: changing the approach to defining vaccine safety and efficacy. Lancet Infect Dis. 2018;18(1):333–8.
20. Katzelnick LC, Gresh L, Halloran ME, Mercado JC, Kuan G, Gordon A, et al. Antibody-dependent enhancement of severe dengue disease in humans. Science. 2017;358(6365):929–32.

21. Dyer O. Philippines halts dengue immunisation campaign owing to safety risk. BMJ. 2017;359:j5759.
22. Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, Machabert T, et al. Effect of dengue serostatus on dengue vaccine safety and efficacy. N Engl J Med. 2018;379: 327–40.
23. Saez-Llorens X, Tricou V, Yu D, Rivera L, Jimeno J, Villarreal AC, et al. Immunogenicity and safety of one versus two doses of tetravalent dengue vaccine in healthy children aged 2–17 years in Asia and Latin America: 18-month interim data from a phase 2, randomised, placebo-controlled study. Lancet Infect Dis. 2018;18(2):162–70.

Integrating the Veterinarian Scientist to the One Health Concept

18

Manuel Moro

One health is the integrative effort of multiple disciplines working together to attain optimal health for people, animals, and the environment. There is a pervasive conviction that human health is far removed from animal health, and many people may wonder how a veterinarian who works with large animals can help contribute to pursuing the goal of better healthcare for humankind. Yet, it should be remembered that a wide range of different species of domestic and laboratory animals are used for the benefit of humanity, and we rely quite heavily on the development of animal models of human disease to advance our knowledge.

One health is thus at the intersection of human, animal, and environment health, and in the one health paradigm, these three different domains merge into one superposed and universal goal. The challenge lies in succeeding to make the one health concept a reality. Indeed, the idea is not new and has existed since the German physician, Rudolph Virchow (1820–1902), coined the term zoonoses (transmission of diseases from animals to men) and originally launched an idea similar to one health. He stated: "between animal and human medicine there is no dividing line—nor should there be. The object is different, but the experience obtained constitutes the basis of all medicine."

In the last 30 years, the number of outbreaks around the world has been increasing, in terms of total number and diversity of outbreaks and the richness of pathological agents [1]. Knowing the origin of these outbreaks is important to ensuring appropriate capacity to respond to potentially pandemic threats. Approximately 60–70% of emerging and re-emerging pathogens are coming from animals. This is due to a range of factors, including global warming, ecological change, globalization, and migration. Examples of these agents and the ongoing disease outbreaks across the world include Middle East respiratory syndrome coronavirus (MERS-Cove), Zika virus, yellow fever, and Lyme disease in North America. Although we

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_18

may be able to develop vaccines for most of these pathogens, there is a compelling need now to understand the epidemiology of these diseases, including the role of animals as disease reservoirs to adequately plan for outbreaks.

Another area that veterinarians have been working on actively is antimicrobial resistance (AMR). AMR represents a major threat to global health, and the use of antibiotics to feed animals is particularly worrisome as it may lead to increased AMR. In this regard, the European Medicines Authority (EMA) reports annually on sales of veterinary antimicrobial products in the European Union, but the bacteria and antibiotics of interest may differ between veterinary and human health, and valuable information may go uncaptured [2]. Furthermore, national surveillance efforts to monitor resistant bacteria remain heterogeneous, precluding accurate comparison across nations, and as Schrijver et al. point out, it would currently appear that the one health concept, particularly as regards AMR detection in humans and animals, is not well reflected in current veterinary or human surveillance systems [3]. Nonetheless the progressive phasing out of antibiotics in animal foods around the world has been achieved through active collaboration of physicians and veterinarians, leading us to hope that this continued interaction will help align human and veterinary medicine with the objectives of the one health paradigm.

Through history influenza outbreaks have had devastating effects on humanity. Although most of the outbreaks have originated from human strains, animals, especially swine and avian species, may play an important role in the generation of new strains capable of infecting humans and in some cases resulting in significant outbreaks. The H1N1 influenza pandemic of 2009 or so-called swine flu was the first pandemic of the twenty-first century. Although dubbed "swine" flu by the media, the H1N1 virus is a combination of avian, swine, and human influenza A viruses. It first emerged in the USA and Mexico and then began sustained human to human transmission, with rapid global dissemination. Fortunately, excellent surveillance infrastructures and good communication between the health authorities of both countries enabled rapid implementation of actions to contain the pandemic, with ample collaboration between physicians, veterinarians, epidemiologists, health workers, and others. The pandemic influenza disease activity peaked in late 2009 and rapidly moved into the post-pandemic phase and fears that the H1N1 pandemic would rival the great flu of 1918 turned out to be unfounded.

Despite the success achieved in containing the pandemic, several areas have been highlighted where there may be room for improvement in preparing for future pandemics of similar or greater magnitude. Firstly, the moniker widely used in the press, namely, "swine flu," led people to assume that the virus affected exclusively swine, and this resulted in huge loss of income for the pork industry, particularly in the USA and Mexico, where sales dropped substantially on the back of bans on import of pork from Mexico or the USA implemented in 17 countries. Mexico alone had a pork trade deficit of $US27m by the end of 2009 [4]. The misnomer also led to draconian, nonscientifically based eradication of swine herds in number countries, further affecting the industry.

In the wake of the H1N1 pandemic, Canada, Mexico, and the USA recognized that the risk of another future pandemic persisted and that the emergence and spread

of influenza viruses with potential cause a human influenza pandemic were an ongoing threat. Thus, the three countries undertook to strengthen their preparedness for such a case and came together to prepare the 2007 North American Plan for Avian and Pandemic Influenza. The plan includes a comprehensive approach to prepare for pandemic influenza in North America based on the assumption that a pandemic was likely to start outside of the region and focused primarily on avian influenza because of the re-emergence of highly pathogenic avian influenza H5N1 virus in humans in 2003. The lessons learned from the H1N1 pandemic have helped to encourage a multi-sector cooperative approach and allow improved preparedness and capacity for response [5], using the one health concept.

References

1. Smith KF, Goldberg M, Rosenthal S, Carlson L, Chen J, Chen C, et al. Global rise in human infectious disease outbreaks. J R Soc Interface. 2014;11(101):20140950.
2. Tacconelli E, Sifakis F, Harbarth S, Schrijver R, van Mourik M, Voss A, et al. Surveillance for control of antimicrobial resistance. Lancet Infect Dis. 2017;18(3):e99–106.
3. Schrijver R, Stijntjes M, Rodriguez-Bano J, Tacconelli E, Babu Rajendran N, Voss A. Review of antimicrobial resistance surveillance programmes in livestock and their meat in Europe, with a focus on antimicrobial resistance patterns in humans. Clin Microbiol Infect. 2017;24(6):577–90.
4. Rassy D, Smith RD. The economic impact of H1N1 on Mexico's tourist and pork sectors. Health Econ. 2013;22(7):824–34.
5. Fineberg HV. Pandemic preparedness and response—lessons from the H1N1 influenza of 2009. N Engl J Med. 2014;370(14):1335–42.

Stressing the Importance of Adult Immunization: Suggestions for How to Change the Paradigm

19

Fiona Ecarnot

From 24 to 26 May 2017, the European Interdisciplinary Council on Ageing (EICA) and the European Union Geriatric Medicine Society (EUGMS) brought together a group of key opinion leaders and stakeholders from the healthcare field in its widest sense, for a conference entitled "Changing the Paradigm: Stressing the Importance of Adult Immunization." The meeting was planned in the framework of the World Health Organization (WHO) concept of healthy ageing as "the process of developing and maintaining the functional ability that enables well-being in older age." Indeed, rather than focusing on simply the absence of disease, healthy ageing goes beyond that and should be considered from the perspective of a person's functional ability, with a view to enabling older people to be and do what they have reason to value. The pillars of promoting health and disease prevention over the life course are nutrition, physical activity, smoking cessation and, last but certainly not least, vaccination. The specific objectives of this meeting convened in San Servolo, Italy, were to review vaccine-preventable diseases (VPDs) and vaccine performance in older adults and analyse the impact of the adult vaccination campaigns currently being implemented in Europe. The meeting aimed to achieve, in light of the data presented, an understanding of the challenge that vaccine hesitancy or scepticism represents, and how existing barriers to vaccine uptake may be overcome, particularly through policy change at a European level. The diverse backgrounds of the participants in the conference enriched the debate, bringing forth truly multidisciplinary and multistep suggestions for actions that could be undertaken to move vaccination forwards in terms of public acceptance and political willingness.

After a range of informative presentations on the current state of VPDs and vaccination practices throughout Europe and the world, the participants worked in small, multidisciplinary breakout groups focusing on various important aspects in

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_19

the vaccine debate. The results of these sessions brought forth a range of useful and relevant actions that could be undertaken to advance the cause of adult vaccination at a European level and are summarized below.

19.1 Public Health and Economy

The group focused on public health and economy discussed several aspects of vaccination.

It is clear that long-term care is a relevant "entry point" where older people should be asked to receive vaccination, and possibly also their relatives could be approached for consent, in order to enhance protection of the community. Another relevant route towards vaccination is the general practitioner (GP). It is clear that making vaccination compulsory may be a problem as regards the ethical questions raised by the patient's right to self-determination, apart from certain obvious cases. In this regard, the "population pathway" aspect of vaccination should be considered.

The following keywords emerged from this session:

- *Coalition* of the different actors in promoting vaccination as part of healthy ageing, considering in particular the need for public trust in the safety and efficacy of vaccines.
- *Awareness* in public health terms of the relevance of vaccination as a welfare-improving and cost-saving instrument. This awareness can be raised by educating the community at large.
- *Transparency* will ensure that all the aspects are fully discussed and that the public does not fall into the trap of misinformation.
- *Enhancing* the community and public health message that vaccination is not just for yourself but for all those you care for.
- *Protecting* people at high risk who can be reached, such as those entering nursing homes and receiving long-term care.

19.2 Long-Term Care

From the point of view of vaccination, long-term care represents a key subset of populations, because it is the area where the cost-benefit ratio of vaccination is most favourable. There is wide variety among the long-term care models around the world, with different levels of long-term and home care across countries. However, one important action that could be implemented across all models would be obligatory vaccination for all older subjects entering into long-term care. In addition, it seems imperative that all healthcare workers and home care providers be vaccinated against infections such as influenza and pneumonia. Indeed, a pair-matched, cluster-randomized trial of staff influenza vaccination in nursing homes showed a 20% reduction in mortality and a strong and significant correlation between staff

vaccination coverage and all-cause mortality in residents (aged 60 and over) when the influenza vaccine was administered to volunteer staff after a face-to-face interview. In addition, in the vaccination arm, there were significantly lower levels of influenza-like illness among residents (−31%), and sick leave among staff was also 42% lower. Therefore, it is clearly of paramount importance that healthcare workers in contact with older subjects on a regular basis be vaccinated against VPDs, particularly infections with potentially serious complications, such as influenza and pneumonia.

19.3 Geriatric Medicine: Preventive Aspects, Acute Medicine

Five key points were identified in this area that are determinant for vaccine uptake in this context.

Firstly, access to vaccines for the older patient. Potential solutions were proposed, such as home nurses or vaccine administration by the pharmacist in the local pharmacy. This obviates the need for temperature control of the vaccine, and most older people attend a pharmacy regularly anyway, with pharmacies widely available in almost all areas. Another facet of the access problem is the funding, since patients who have to pay for a vaccine out of their own pocket may be more reluctant to get it.

Secondly, there is a pressing need for harmonization of recommendations within Europe. Indeed, the United States advisory committee on immunization practices is a highly influential body in the US healthcare landscape whose recommendations enjoy high uptake rates among GPs. There is no analogous body at the level of the European Union, which would have sufficient weight to make recommendations for the whole of Europe that would be widely followed by GPs and other healthcare providers. Perhaps the creation of a pan-European advisory committee with the mandate to issue recommendations would help to standardize vaccine practices and integrate adult vaccination into the healthcare pathway of patients across Europe.

The third point is a natural corollary of the second, namely, registries to record vaccine uptake, since it is impossible to track performance in terms of vaccine prescriptions and administrations without regular exhaustive recording. In addition, the variety of providers that can give vaccines (GPs, specialists, etc.) and the heterogeneity of administrative environments (electronic vs. paper health records) render recording in registries a necessary step to achieving recommended uptake thresholds and evaluating performance.

Fourthly, advertising and acceptance of vaccines need to be improved. Public health campaigns targeting the general public need to focus on making citizens understand that vaccination must be a part of the normal things you need to do. This involves raising every subject's level of knowledge so that they know they should be getting vaccines. This necessarily involves a change of mindset, and the example of the USA is illustrative of this. Because vaccination can now be performed in pharmacies throughout the USA and because there are advertisements in pharmacies everywhere, the pervasive idea that it's the GP's job to worry about vaccination is

now receding, and the population are gradually coming round to the idea that it's every individual's own responsibility to get their vaccines. Another successful example is the vaccine uptake rate above 99% achieved in Taiwan, where every patient knows they should be going to their health provider and asking for vaccines on a regular basis. News media and public announcements are an important vector for advertising and general awareness. Resistance from both doctors and patients is a challenge, and this can be overcome by spreading the vaccine-friendly public health message consistently and regularly to achieve a change in practices and culture among the target groups.

Finally, advice to policy-makers must be anchored in cost-effectiveness, since programmes that are cost-effective in one country may not be so elsewhere. In this context, there is a compelling need for accurate figures from all countries, to inform decision-makers about how best to determine vaccine budgets at a national level and taking local conditions and specificities into account.

19.4 Pharmacy Group, Nurses and Health Visitors

The Pharmacy Group of the EU, presided by Rajesh Patel, is an association of 34 member states that brings together 400,000 pharmacists and 160,000 pharmacies in Europe. As qualified professionals, pharmacists are a prime target to implement vaccine programmes among the population.

Three main questions arise in relation to vaccination practices. Firstly, what hindrances exist to vaccination within a community? First among the barriers to vaccination is scepticism about the integrity of the pharmaceutical industry. Many people labour under the false impression that because the industry turns over a healthy profit, they must have something to hide. Clearly, there is a need for education of the public to dispel false ideas. There is also some scepticism about the capacity of professionals other than physicians to give vaccines. There again, public information campaigns can help to raise awareness about who can and cannot vaccinate and make potential patients confident that their health provider can perform the task competently. In the same vein, negative media stories relating to vaccines that may affect patients' attitudes need to be countered by disseminating positive and evidence-based information. Ideally, education should start at a young age, not just by educating parents for their children but also by integrating vaccination into the curriculum of the initial university studies for all allied health professionals.

A second question, and this might be considered the reverse side of the "barriers" coin, concerns incentivization: what incentives exist for patients in the EU member states to get vaccinated? Clearly, uptake rates will be lower when the patient has to pay for the vaccine out of their own pocket. For example, 4 years ago in the United Kingdom (UK), patients who needed the influenza vaccine had to pay for it, and approximately 300,000–400,000 patients were vaccinated. The following year, vaccination became part of the National Health Service (NHS), and all providers received the same fee giving the vaccine. That year, 750,000 patients got vaccinated, and, in the second year of free availability, 1.2 million patients were

vaccinated. Estimates project that over 2 million patients will be inoculated in pharmacies this year, for the influenza vaccine alone. Evidently, accessibility is a major determinant, and creating a mindset whereby the patient can just stop into the pharmacy and get the vaccine anytime it's convenient for them could help to boost uptake rates. In addition, this easy access system could be extended to other health professionals.

Thirdly, and in line with the key messages underlined by the other groups, global policies must be influenced. Local initiatives in favour of vaccination will remain fruitless if there is no will from their paymasters or from their national health executive to implement a wider vaccination strategy. It is therefore incumbent on leaders of organizations to lobby and educate governmental organizations so that vaccines are prioritized. Shared best practice between member organizations can help to bridge gaps in knowledge, and organizations that have taken initiatives (successful or otherwise) to improve vaccine uptake should share their experiences through public reporting, in order to inform those who are new to the field and looking to implement effective measures. Shared knowledge and learning from our peers in other countries and medical settings can lend weight to the movement and help gather the momentum required to influence policy-makers.

19.5 Non-governmental Organizations (NGOs)

In the current economic climate, it is an undisputable fact that resources—both human and financial—are limited, no matter what policy or programme is on the agenda. In this context, educating people about vaccines is important but so is having people available to produce, market and administer them. Around the world, the majority of patients who are hospitalized for infectious diseases are aged under 2, or over 65, and vaccines are most beneficial in this high-risk groups. The changing role of people in society contributes to this situation, with more parents working outside the home and putting their children into collective childcare facilities and more grandparents minding small grandchildren to relieve the financial burden on their working children. Similarly, the increasing presence and importance of social media in modern lifestyle has both positive and negative effects, as they reach a very wide audience, but not always with the right message. NGOs can be a strong voice in favour of vaccines, and using social media to spread impartial and evidence-based information about vaccines to a wider audience is a promising means of communication.

There are many barriers to be overcome on the path to improving vaccine uptake. Scepticism and lack of trust in government and industry are just some of these obstacles. In addition, there is a lack of harmonized schedules, with extraordinary variation in vaccine recommendations around the world. More coherent vaccine schedules are sorely needed, although they will have to be different in some respects between continents for a variety of reasons (including lifestyle, cultural and genetic factors). In this context, the WHO regional offices might have an important role to play in providing particular vaccine schedules to special parts of the world.

With harmonized vaccine schedules in hand, the next step is to identify at-risk groups and the vaccines needed and target individual vaccines to improve communication. To take this beyond a local or regional level campaign, there needs to be a strong political will, with proactive rather than reactive implementation. Bringing the questions of vaccination into the political arena could help to bring about the culture change that is needed for adult vaccination. Paediatric vaccination is a resounding success story, and NGOs can help to replicate this success with adult vaccination. Education needs to start young, in schools, for example, making use of today's modern media, to reach the widest possible audience. Incentives to GPs and the removal of any financial impediments to receiving a vaccine will help to make inoculation accessible to all, while healthy ageing campaigns and personal health records can help to integrate adult vaccination into the routine healthcare of all adults. Finally, production of vaccines also needs to follow suit, as increases in manufacturing capacity will be necessary if the campaigns are successful. There needs to be sustained production of vaccines around the world also to ensure pandemic preparedness. NGOs have a pivotal role at all the stages of the vaccination pathway, from proof of efficacy, to production, distribution and monitoring.

19.6 Pharmaceutical Industry

The pharmaceutical industry is a key player in the quest to improve adult vaccination, and they have a major interest in proving to the public, payers and policymakers that vaccines are a good investment. This can be shown by providing solid evidence in support of the efficacy, safety and cost-effectiveness of vaccines. This is highly relevant data that needs to be collected in a systematic and standardized manner. In terms of pharmacovigilance, for example, it is insufficient to rely on spontaneous reporting of potential adverse reactions or events. Regular registries collecting all data of interest in a systematic manner, across several nations, will help to generate reliable, representative and evidence-based data.

Another stumbling block is the multiplicity in decision points, particularly in Europe, for example. In the EU, healthcare is devolved to the individual member countries, of whom some further pass the responsibility down to regions. Therefore, when it comes to implementing policies, it is highly complex and incoherent. It would be desirable to simplify the chain of decision-making so that political will at the top of the hierarchical chain to provide vaccination in an older population can become a uniformly implemented reality across the EU.

Finally, a point that more particularly concerns the pharmaceutical industry is the potential shortage of vaccines. In case of a pandemic, for example, it is quite likely that shortages in vaccine supplies would occur. Indeed, such shortages have occurred in the past, because of changes in business plans. For example, if a company pulls out of the market, the burden falls on the other companies to meet the demand. Similarly, if there is a quality problem with the product, the production line stops, and there are suddenly no more vaccines being produced. Solutions to these

potential problems need to be envisaged. Stockpiling is not an option if the shelf life of the vaccine is short. In fact, shortage may be unavoidable because of the complexity of production processes and might require incentives from governments to manufacturers to ensure a constant supply. The pharmaceutical industry needs to be included as a full partner in discussions about vaccine implementation, as it is an instrumental partner in delivering the service in the field.

19.7 Media and Science

The main point to come out of these breakout sessions was that nowadays, the media encompasses everything—anything that transmits a message can be considered as media, and, in today's world, they are omnipresent: from the more traditional posters in waiting rooms, newspapers, TV and radio to Facebook, Twitter and Instagram pictures of Hollywood stars having their babies vaccinated.

Why should we bother with the media at all? Because it is necessary and instrumental, and it can leverage the media as part of a wider strategy to reach policy-makers. The media can be successfully used to overcome myths and hesitancy among the public, but, to do this, we need to engage in all media types. They can be instrumental in achieving vaccination goals. By putting a new narrative out there in the public domain via social media, it will get voters talking about vaccine, and that makes it easier to get politicians to listen and take the message on board.

One might also ask why social media are so hostile to vaccination or why their message is so often negative. However, these questions are off the mark, because at the outset, technology is neutral, and it is only how you use it that determines whether it is ultimately good or bad. Clearly, the media are somewhat sensationalist, but lobbyists such as the anti-vaccine campaigners, who have a message that they are determined to spread, may be likened to soldiers: they are coordinated and organized and present a simple but unified message. If an adverse side effect becomes known, they prepare quotes and put information out to journalists quicker than the pro-vaccine group. Therefore, advocates of adult vaccination need to coordinate their activities and provide a single, emotive message to counter that of the anti-vaccine lobby. Each country will need to decide what messages resonate best within their community, but some messages are universal. For example, principles of behavioural economics show that when you thank people for a certain (desired) behaviour, they are more likely to adopt it (e.g. thank you for buying a bus ticket, rather than a menacing message of impending sanction if you don't buy a bus ticket). Similarly, behaviours can be changed for the sake of other people, such as children saying to their parents, "Daddy, you haven't got your seatbelt on". Patients will do something if they think it is important and for the benefit of their loved ones, and this can be applied to vaccination too. These avenues are all potential action areas for spreading the pro-vaccine message. And when the next news story breaks about vaccines, we need to know what to do about it and what alternative message to put out there via every available media.

19.8 One Health and Adult Vaccines

The One Health concept is a movement to forge equal and all-inclusive collaborations between physicians, veterinarians, dentists, nurses and other scientific health and environmentally related disciplines. One might ask: what is the contribution of veterinary and One Health approaches to the control of human communicable diseases? Veterinary medicine is rich and highly active in the identification of infectious diseases in animals and also in the control of these diseases. According to the terms of an agreement signed in 2010 between the World Organisation for Animal Health (OIE) and the Food and Agriculture Organization of the United Nations (FAO), three groups decided to share their experiences in the control of emerging new disease through early detection, wide information, international sharing of data, implementation of sanitary rules and budgets allowing management of policy and control of communication. This latter point includes control of communication towards farmers, towards veterinary services and also towards the media. Clearly, veterinary medicine is able to give some fine examples not only of the control of emerging diseases in animals but also of the cooperation that exists between human health organizations like the WHO and animal health organizations such as the OIE.

A second question addressed in this breakout session concerned the role that veterinary medicine can have in increasing adult vaccination uptake. Here again, veterinary medicine can give examples of emergence of new disease, for example, according to climate warming. Lyme disease is a prime example. Veterinary medicine can also demonstrate the risk of introducing infectious disease into countries, despite existing sanitary rules. Indeed, every year, there are cases of rabies or other diseases occurring, because people travel abroad and bring back infected animals, who transmit disease to humans. This knowledge can help human medicine authorities and often appears on the veterinary radars first.

Thirdly, the experts in this group discuss the impact of antibiotic use in animals on antibiotic resistance in humans. There are exorbitant amounts of antibiotics used in both human and veterinary medicine, and this may be dangerous for the emergence of antibiotic resistance. There are some good examples of sanitary plans to reduce antibiotic use, such as the French national plan to reduce animal antibiotic use, aimed also at limiting the use of critical antibiotics. In this regard, a coalition between dentistry, veterinarians and human medicine would be useful to be aware of problems and pool knowledge.

Finally, the One Health concept is not well known. In many countries, veterinary medicine is not heavily involved in human medicine discussions or policy, and many people (politicians included) are surprised at the idea that veterinarians could contribute to the management of human health. This group proposes that the medical curriculum for doctors and the undergraduate training of veterinarians should include a few hours of courses dedicated to One Health, to underscore how human and veterinary medicine can cooperate for the benefit of human health.

19.9 Conclusions

The European Interdisciplinary Council on Ageing has a main mandate to create alliances between and among different stakeholders, and the stakeholder's meeting held in San Servolo from 24 to 27 May 2017 was a first step towards this goal on a topic that is critical for the geriatric community. Clearly, there are difficulties in communication and in working together, but it is encouraging that the most common words cited after all the breakout sessions were cooperation and alliance, and this could be considered the take-home message from this important meeting. From a practical point of view, representatives from scientific societies, NGOs, the pharmaceutical industry and the public need to agree on general strategies and actions to be taken, to which we must then adhere and do our best to put them into practice. We need to roll out a comprehensive action plan to achieve our objective of creating a programme for disease prevention and health promotion for older populations.

How Can We Integrate Life Course Vaccination into the New WHO Definition of "Healthy Ageing"?

20

Jean-Pierre Michel, Fiona Ecarnot, and Jane Barratt

The first global report on health and ageing published by the World Health Organization (WHO) in 2015 introduced a new and innovative concept, namely, the idea that healthy ageing encompasses more than just the absence of disease [1]. Indeed, the report considered healthy ageing to be a more holistic process of developing and maintaining the functional ability that enables well-being in older age. There are two major components to this concept, namely, personal and environmental determinants of ageing. The personal determinants of ageing are what we call our intrinsic capacity. This comprises our genetic inheritance, our personal characteristics, and, importantly, our health characteristics, such as the presence or absence of disease, health-related behaviours, risk factors, etc. So at an individual level, our intrinsic capacity is the composite of our personal mental and physical capacities. These capacities are put to use when we live daily lives in our given surroundings, and this creates opportunity for the environmental determinants of ageing. Indeed, the interplay between our intrinsic capacities and surroundings yields our functional capacity.

Over the course of one's lifetime, since ageing is a lifelong process, there is an initial period of high and stable capacity, where the individual strives to reach their maximum functional ability and maintain it at that level for as long as possible. Ideally, we seek to create an environment that enables a person to do what they value, for as long as possible. The means to achieve this is related to various aspects such as education, lifelong learning, psychosocial adaptation, the presence of a supportive environment, access to affordable healthcare, and interacting in the

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_20

social system. All of these factors interplay with, not to say drive our ageing process, and may help or hinder us on our way towards the main goal of living independently in our own surroundings for as long as possible, ideally until the end of life. However, as age advances, there is a decline in both intrinsic capacity and functional ability, often leading to a significant loss of capacity towards the end of life. Nonetheless, the literature is replete with reports of what we can do to maintain and, at times, improve function across the life course.

In study of 19,064 participants from the US Health and Retirement study examining the percentage of participants who met various definitions of "healthy ageing", 73.4% were free of major disability, while almost 97% were free of cognitive impairment [2]. Ideally, high proportions of subjects would live to be very old without disability, but there is a need to consider the challenges that this entails for healthcare systems. Promotion of health is essential during the phases when intrinsic and functional capacity are at their peak. This includes education, to create high cognitive reserve, adequate and healthy nutrition, moderate and regular physical exercise, and refraining from smoking and excessive alcohol consumption, and the message needs to be repeated by lifelong public health campaigns.

Results from an increasing number of randomised controlled trials (RCTs) show that it is possible to prevent or delay the onset of chronic diseases and to temper the negative impact of disease on daily functioning. These include cardio-, neuro-, and nephro-vascular diseases, as well as the leading geriatric health issues such as cognitive decline, dementia, musculoskeletal disorders, and sensory impairments. There is a need to continue ongoing research in order to demonstrate with RCTs that interventions in midlife can have significant beneficial impacts on later life. Furthermore, at a later stage in the life course, preventing or delaying malnutrition and sedentary habits is also important, as, together, they are linked to sarcopenia and frailty, which in turn can lead to functional decline. Indeed, there is evidence in the literature showing that a substantial proportion of hospitalised patients in European hospitals eat less food than provided and survivors of the hospital phase are even more malnourished after discharge than before admission [3, 4]. Therefore, the importance of malnourishment must be stressed, as it is a downward spiral from which it is difficult to escape. Towards the later periods of life, global geriatric assessment has a key role to play in identifying the health status of older adults, and indeed, it is a main tool among the geriatrician's armamentarium. It is vital to come to agreement on objectives for care with the patient and family and to establish a management plan that can be reviewed regularly, keeping in mind the results of interventions or actions undertaken thus far. This is quite simply the essence of geriatric medicine, and it covers physical, mental, functional, and social aspects.

Considering a person within their community or in the hospital requires a vision of an age-friendly community that removes the barriers to participation in society, as well as compensating for any loss of capacity. The concept of an age-friendly environment encompasses a range of aspects, such as transportation and housing, outdoor spaces and buildings, community support and health services, communication and information, civic participation and employment, social participation, respect, and social inclusion [5].

Finally, we also have to think about long-term care, which calls for a humanistic approach. Long-term care at home or in an institution includes a range of services and support for coping with personal care needs, not specifically medical care, but for basic personal tasks of everyday life. Towards the end of life, we would all hope to have dignity-conserving care [6], namely, care that conserves or bolsters the dignity of the dying patient. However, there are four persisting problems with this. First among these is access to healthcare, since many patients are unable to access healthcare due to its cost, ranging from less than 5% of patients in France to almost 20% of patients in the USA. Secondly, coordination of care is often suboptimal, causing problems for the healthcare trajectory of up to 40% of patients. Frequent, timely, and accurate communication, as well as problem-solving, shared goals, shared knowledge, and mutual respect among healthcare providers, is the foundation on which successful management is built. Thirdly, if there is an absence of political prospects, then the financial and social support and the public health initiatives will not be put in place to enable senior-friendly commitments and the development of a culture of geriatric medicine to deliver age-friendly healthcare. Finally, there are a number of ethical issues in end-of-life care and research that are beyond the scope of this report.

Despite all the potential areas suitable for intervention over the life course, there remain major gaps along this pathway, namely, vaccination. Across the spectrum of the life course approach to health and healthy ageing, we failed to mention the adult vaccine "hole" or "gap" or vaccination for the elderly or healthcare workers. Within the definition of healthy ageing, vaccines and the life course approach to vaccination has a major role to play that needs to be reinforced, so that it becomes as natural a part of ageing as getting glasses when your sight fails.

In conclusion, as underscored by the WHO definition, healthy ageing is more than just the absence of disease. It includes maintaining functional abilities at the highest level, building and maintaining intrinsic capacity, and in this way, achieving the optimal outcome of living in functional independence in our own surroundings until the end of the life. In this context, teaching geriatrics to all categories of healthcare professionals is an urgent medical priority with important socioeconomic implications.

References

1. World Health Organisation. World Report on Ageing and Health Geneva. 2015. Report No.: 3.
2. McLaughlin SJ, Jette AM, Connell CM. An examination of healthy aging across a conceptual continuum: prevalence estimates, demographic patterns, and validity. J Gerontol A Biol Sci Med Sci. 2012;67:783–9.
3. Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364:1293–304.
4. Hiesmayr M, Schindler K, Pernicka E, et al. Decreased food intake is a risk factor for mortality in hospitalised patients: the NutritionDay survey 2006. Clin Nutr. 2009;28:484–91.
5. World Health Organization. Global age-friendly cities: a guide. Geneva: World Health Organization. 2007. http://www.who.int/ageing/publications/age_friendly_cities_guide/en/.
6. Chochinov HM. Dignity-conserving care—a new model for palliative care: helping the patient feel valued. JAMA. 2002;287:2253–60.