FEAM
Federation of European Academies of Medicine

Immunisation for old adults in Europe: scientific and social strategies

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Foreword

Dear reader,

There is a call for a life-course approach to disease prevention and health promotion, which includes vaccination across the age spectrum. Adult vaccination programmes in many countries, including Europe, are complex, often lack prioritisation and funding. The reasons for such complexity are various, including inconsistency or complete absence of national vaccination policies and cost barriers. Furthermore, there is a failure among older adults and healthcare workers to recognise potential benefits of vaccination for the older population, often considered only for children. Important scientific gaps also remain; we need a better understanding of adult immunization in light of the gradual decline of the immune system associated with ageing ('immunosenescence'). The high prevalence of comorbidities including malignancy and its treatment as well as the frequent use of immunosuppressors among older adults further complicate this landscape.

Support for emphasis on and consistency of adult vaccination strategies, throughout Europe, have been voiced by various experts and groups. While the scientific consensus is that a life-course approach to ensure optimal vaccine uptake across all ages reduce morbidity and mortality in later life. Clearly for these benefits to materialize, vaccines need to be recommended and used. Furthermore, questions about adult vaccination have acquired more urgency in the light of the COVID-19 pandemic.

In view of the great importance of these issues, the Federation of European Academies of Medicines (FEAM) convened an expert committee with the aim of examining some basic parameters of immunosenescence and challenges to the current situation of adult vaccination in Europe.

Our main objective is to emphasise the vital importance of vaccination in old age. This report is also building on a previous FEAM/EASAC work, a commentary published in 2018, to respond to the European Commission's attempt to strengthen cooperation against vaccine preventable diseases.

We thank the members of the expert group for their guidance and for their continuing commitment to support the project and share their expertise. We wish you a pleasant reading and welcome discussion of any of the points raised in our report.

George Griffin
Immediate Past President of FEAM

Executive Summary

Vaccines are one of the best life-saving interventions developed, and they have been a revolution for modern medicine by preventing the spread of infectious diseases and related deaths. Vaccines are a principal tool for the primary prevention of communicable diseases, being highly efficacious and cost-effective. Promoting life-course vaccination programmes, thus is essential for the wellbeing of the whole population. The importance of such programmes is underpinned by the knowledge that vaccines not only impact mortality but also treatments of non-communicable diseases (NCDs), disability prevention, antibiotic usage, thus reducing antimicrobial resistance (AMR). The significant positive cardiovascular protection provided by influenza vaccine was also recently confirmed, and such secondary side effects deserve to be understood and more widely promoted.

Despite the highly significant role that vaccines play in global health, concerns over their safety and the heterogeneity of distribution worldwide have increased tremendously over the years. In the European Union, each country develops its own life-course vaccine recommendations which are less divergent for children than for older adults. A survey distributed by the Federation of European Academies of Medicine (FEAM) in Spring 2021, assembled data from European Academies about current national adult vaccination schedules. This data clearly highlighted significant differences in vaccination policies in terms of age qualification, vaccine components, frame of implementation and reimbursement procedures. Lack of consensus for some immunization schedules was also noted as important issue, as such behavior leads to reduced confidence in the entire adult vaccination programme.

The aging immune system or immunosenescence is thought to be a major risk factor for the higher incidence and prevalence of chronic conditions, like cardiovascular diseases, metabolic diseases, and neurodegenerative diseases. In the older population, these conditions are often clinically presented as multimorbidity that may lead to organ failure and death. With the advance of immunosenescence, older adults also become more susceptible to infectious diseases and cancer. In practice this means that immunological responses must be checked in the clinical trials involving old people, and vaccination schedules to be adapted accordingly. In the absence of immunosenescence-reversing agents and biomarkers, active research is now required to identify new molecules that may guide vaccination strategies. Alternative approaches to accommodate this global deficit might also include vaccines with adjuvant activity, to overcome higher thresholds for activation, vaccines with different antigenic loads, and vaccines with different delivery routes or dosing intervals. In general, the effects of aging may be overcome with vaccines tailored to old age. For instance, vaccines with adjuvant effects are likely to enhance immune response.

Likewise, the immune response to mRNA vaccines appears to be less vulnerable to ageing effects. The immune response is surprisingly good also when using new potent vaccines against herpes zoster, hepatitis B and COVID-19 that provide adequate protection in ageing patients, however the responses appear to be waning sooner. All of this suggests that vaccines can be improved to be optimal and highly relevant for old individuals. Particularly, the mRNA vaccine technology is rapid, flexible and facilitates a scalable manufacturing process. For example, mRNA vaccines against SARS-CoV2 proved their efficacy in young, but also in old populations. The impressive and unexpected efficacy of this new generation of vaccines opens the way to encourage a more global advance in vaccine research and thus helps achieve an overall better immunological protection for old people.

Following the reported cluster of COVID-19 in Wuhan City - capital of Hubei province - in China, the first preventative vaccinations against the novel coronavirus already highlighted the crucial importance of shifting towards an equitable global distribution of developed vaccines. At present, the scope of global COVID-19 vaccine inequity is immense, and data collected in this regard must not overshadow the importance of an

equal access to health education and promotion among world countries. These variations in vaccine distribution globally create populations of vulnerable patients in those countries, which has global effects. When a medicinal drug or new treatment enters clinical use after regulatory approval, there is an unavoidable gap in knowledge regarding vaccination in those patient groups, such as immune-compromised patients. In parallel with the entry of the vaccine into regular use, data on the immune response of compromised patients should be accrued.

Vaccine hesitancy is another crucial societal issue that is addressed in this report. Vaccine-hesitant individuals are a heterogeneous group, who refuse all or some vaccines, arguing doubts about safety and efficacy. They are vulnerable to misinformation and fake news, while they seek information to actively confirm their concerns. European policies that promote studies on the quality, efficacy/effectiveness and safety of vaccines in old adults are now needed. Influenza vaccine coverage rate for chronically ill young and old adults - for example after organ transplantation or chemotherapy - is extremely unsatisfactory in the EU, but even so, paradoxically, remains higher than coverage among healthcare professionals. Very often, due to a lack of appropriate vaccine education, healthcare professionals may lack confidence in the efficacy of the vaccine, or not fully appreciate the positive effects of vaccines, or the risk of the disease, and the importance of their role in possible transmission. A considerable higher level of education may contribute to higher acceptance and recognition of vaccine's benefits, and it is key to promote the establishment of more inclusive societies that allay fears and address concerns around vaccination efficacy.

In conclusion, this report clearly highlights significant variation among vaccination schedules for old age in the EU and the need to develop a culture of vaccine promotion among the general population and healthcare workers. The Expert Committee that has prepared the following document also briefly summarized the current knowledge of immunosenescence and illustrated ways of enhancing immune response using novel adjuvants and delivery vehicles for vaccine development. Furthermore, vaccine hesitancy leading to refusal is addressed with an emphasis on education for old people and healthcare workers. Multimorbidity in the old population is also discussed as an important factor requiring personalization of vaccination. In addition, ways to improve immune responses to vaccines in old patients with comorbidities are crucial to investigate.

FEAM strongly believes that in the current COVID-19 era, the time is right to increase vaccine diplomacy. Our goal is thus to contribute to the establishment of common immunisation programmes across Europe, and recommendations for promoting "health ageing" are here reported.

Introduction

Significance of Vaccines in Old Adults

Prof. Jean-Pierre Michel
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*"History confirms that vaccines
have been the medical intervention
with the greatest beneficial impact on human health and longevity" [1].*

This strong assertion by Plotkin is confirmed by undisputable data. The toll of communicable diseases worldwide has decreased from 33% of total deaths in 1990 to 25% in 2010 [2]. Due to this tremendous reduction, and before the onset of the current SARS-CoV-2 pandemic, the World Health Organization (WHO) declared that worldwide, vaccines prevent more than 2.5 million deaths from communicable diseases annually [3].

Paradigm shifts gone unnoticed

In this public-health context, it appears important to stress that worldwide, there are now more adults aged over 65 than children aged under 5 years. The number of older adults is set to increase from 0.7 billion in 2020 to 1.5 billion by 2050 [4]. These numbers must not overshadow the importance of health inequities among world countries. Today, in a few African countries (Angola, Niger, and Ivory Coast) life expectancy at birth is 3 decades lower than in European countries testifying why the WHO continues considering old age from the age of 60 years. However, all over the world, the ageing process is extremely heterogeneous, explaining the difficulty of defining universally "old age".

In the following pages, the European working group members considered "old age" over 65 years, knowing that there is a lack of vaccine uptakes at midlife and that only life course immunization programmes will help protect the entire population from vaccine preventable diseases.

As a matter of fact, in the USA, every year, while vaccine-preventable infectious diseases cause approximately 3,000 deaths in children, they are responsible for more than 50,000 deaths among adults [5]. These demographic and public-health imbalances are striking, and reflect a number of underlying structural, economic, cultural and political issues [5]. Furthermore, our understanding of the immune response to vaccines in the old population and ways to boost it are increasing.

Intergenerational transmission of vaccine preventable infectious diseases

Herd immunity occurs when a sizeable enough proportion ($1 – 1/R_0$) of the population becomes immune to an infectious disease (either through vaccination or natural infection) [6]. Herd immunity, also termed "community protection" [7], prevents the spread of infection from person to person within the community. Several studies have demonstrated the impact of community immunity between younger and older generations [8,9]; one powerful example of herd immunity was observed after the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) for all children below the age of 5 years in the USA in 1998. Five-year follow-up clearly showed that the PCV7 vaccine not only drastically decreased the incidence of invasive pneumococcal disease (IPD) in children and a decrease in antibiotic usage, but also led to a significant reduction in the incidence among older unvaccinated adults [10]. Promoting life-course vaccination programmes, thus appears essential for the wellbeing of the whole population [11]. The importance of such programmes is underpinned by the knowledge that vaccines not only impact on mortality, but also on antibiotic usage, antimicrobial resistance, non-communicable diseases, and disability prevention [12].

Vaccines and antimicrobial resistance

An unexpected issue to arise from the introduction of the 13-valent pneumococcal vaccination (PCV13) was its effect on antimicrobial resistance for this organism. In the United States, between 2009 and 2013, decreases of up to 80% in *Streptococcus pneumoniae* resistance to cephalosporins, macrolides, penicillin, and tetracyclines were observed [13]. This makes vaccines an attractive instrument in the fight against antimicrobial resistance, by protecting people against major infectious diseases, such as influenza or pneumococcal pneumonia, thereby reducing the spread of disease and the use of antibiotics [14]. However, this only holds for those bacterial infections for which a vaccine exists, in other words not (yet) for methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococcus sp. (VRE), extended-spectrum beta-lactamase (ESBL), Carbapenem-Resistant Enterobacterales (CRE) and resistant gonococci. All these organisms pose significant health risks to the individual.

Influenza vaccines and cardio- and neuro-vascular health

There is significant epidemiological evidence showing that infections such as those caused by influenza virus and pneumococci are followed by enhanced occurrence of (cardio)vascular complications. Although the mechanisms behind this association have not been elucidated, a persistent inflammatory state after the infection (trained immunity, chapter 2) may play a key role. In line with these observations, recent epidemiological studies testify to the crucial benefits of vaccines. A nationwide cohort study in Denmark including all (134,048) patients over 18 years of age diagnosed with heart failure reported that at least one influenza vaccine shot after the diagnosis was associated with a significant 18% decrease in all-cause death [15]. Study from the Taiwan Longitudinal Health Insurance Database (1996-2008) including 7,722 patients over the age of 55 and suffering from chronic obstructive pulmonary disease demonstrated that, compared to non-vaccinated individuals, those who received the influenza vaccine had a significantly lower risk of hospitalization for acute coronary syndrome [16]. The significant positive cardiovascular protection provided by influenza vaccine was recently confirmed by an interesting meta-analysis [17], and these effects deserve to be better known and more widely promoted. It has also been shown that there is an increased risk of stroke after the clinically proven onset of herpes zoster in adults between the age of 50 and 60 years [18]. Here again, the positive preventive efficacy of herpes zoster vaccination was recently demonstrated by a nationwide cross-sectional telephone survey of 265,568 non-institutionalized US adults aged 50 to 79 years old [14]. After stratification of participants into six 5-year age groups, Cox proportional hazards analysis indicated that those without zoster vaccination were at significantly higher risk of stroke compared to those who received vaccination with the live-attenuated vaccine [14].

In summary, the lack of attention paid heretofore to the positive outcomes of immunization (especially with influenza and pneumococcal vaccine) on cardio-and neuro-vascular events in the ageing population, is extremely damaging.

Another hypothetical impact of vaccines on brain neuro-inflammation

A secondary analysis of the prospective Canadian Study of Health and Ageing focused on a community sample of 3,865 cognitively impaired participants (Alzheimer's disease, AD) aged 65 years and older [19] and investigated whether any links exist between the cognitive status of participants and previous vaccinations, at baseline (1991-2) and during follow up (1996-7). After adjusting for age, the authors found a significant association between a lower risk of AD and exposure to diphtheria/tetanus, polio, and influenza vaccines [19]. Similar observations were made for vaccines used to protect against shingles [20] and Bacillus Calmette Guérin (BCG) (Figure 1) treatment in patients with bladder cancer [21]. These surprising results were the start of the infectious hypothesis of late-onset dementia, which has been the subject of ongoing debate in recent decades [22]. Indeed, in a life-course perspective, the role of infant vaccinations and boosters is fundamentally important [11].

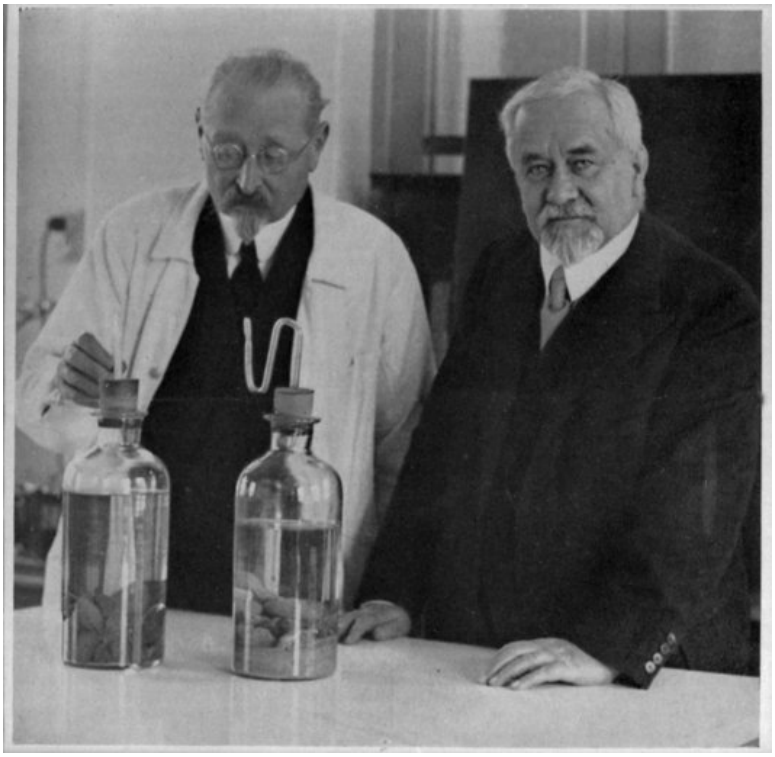

Figure 1. Bacillus Calmette-Guerin (BCG) is a live attenuated form of *Mycobacterium bovis* that was developed 100 years ago as a vaccine against tuberculosis. The figure shows Albert Calmette and Camille Guérin, co-inventors of the BCG vaccine. Note the simple equipment they used for over one hundred passages of *Mycobacterium bovis* in potato broth to produce the initial BCG vaccine strain. RNA technology can now produce specific designer vaccines within 3 months.
Source: http://www.patrimoinehospitalierdunord.fr/biographies-calmette-albert-1863-1933.html

These positive effects of vaccines are tempered by low vaccine coverage rates

In Europe, very few countries, except for the United Kingdom and the Netherlands, satisfied the WHO recommendations (75% of the population of the 65+ population) for annual influenza vaccination [23]. The usual influenza vaccine coverage rate for chronically ill young and old adults is extremely unsatisfactory, but even so, remains higher than coverage among healthcare professionals [24]. Very often, due to a lack of appropriate vaccine education, healthcare professionals lack confidence in the efficacy of the vaccine, or do not fully appreciate the positive effects of vaccines, or the risk of the disease, and the importance of their role in possible transmission. They also have doubts about the low risk of adverse side effects [25]. Lastly, individuals at risk are often not encouraged by physicians regarding the global benefits of vaccination [26]. As there are close relationships between trust in science and vaccine confidence, it appears important to quickly identify factors that contribute to the production of societal consensus around trust in science [27], to develop a culture of vaccine promotion among healthcare workers, which will impact the general population. The success of future vaccine educational campaigns needs to target all healthcare professionals' attitudes and perceptions in all types of workplaces, coupled with strong physician support, encouragement, and leadership [28,29,30].

Towards a more consensual scientific message

In the European Union, each country develops its own life-course vaccine recommendations. These recommendations are less divergent for children than for older adults (as regards vaccine age thresholds, the vaccines recommended, reimbursement by the social security system etc). Two previous consensus statements and guidelines from the two major European societies of gerontology and geriatric (EUGMS and IAGG-ER) associated with the vaccine section of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [31,32] remained unsuccessful. The Federation of European Academies of Medicine (FEAM) strongly believes that in the current COVID-19 era, the time is right to increase vaccine diplomacy [33], following the United Nations initiative "the future we want" [34], to reaffirm our collective commitment to proposing updated and scientifically based recommendations for European adult immunization.

References

1. Plotkin S. History of vaccination. Proc Natl Acad Sci U S A. 26 août 2014;111(34):12283-7.
2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 15 déc 2012;380(9859):2095-128.
3. World Health Organization. Global Vaccine Action Plan 2011 - 2020. [Internet]. Geneva; [cité 25 déc 2020]. Disponible sur: https://www.who.int/teams/immunization-vaccines-and-biologicals/strategies/global-vaccine-action-plan
4. United Nation data. World population by age [Internet]. [cité 24 juin 2021]. Disponible sur: https://data.un.org/Search.aspx?q=world+population+age
5. Poland GA, Belmin J, Langley J, Michel J-P, Van Damme P, Wicker S. A global prescription for adult immunization: time is catching up with us. Vaccine. 18 oct 2010;28(44):7137-9.
6. Philip RK, Attwell K, Breuer T, Di Pasquale A, Lopalco PL. Life-course immunization as a gateway to health. Expert Review of Vaccines. 3 oct 2018;17(10):851-64.
7. Fine, P. E. M., K. Mulholland, J. A. Scott and W. J. Edmunds. Community protection. In: Plotkin's Vaccines. Philadelphia: W. A. Orenstein and K. Edwards. Philadelphia, Elsevier:; 2018. p. 1512-31.

8. Yu-Ann Fang, Chang-I Chen, Ju-Chi Liu, Li-Chin Sung. Influenza Vaccination Reduces Hospitalization for Heart Failure in Elderly Patients with Chronic Kidney Disease: A Population-Based Cohort Study. Acta Cardiologica Sinica. 31 mars 2016;32(3).
9. Reichert TA, Sugaya N, Fedson DS, Glezen WP, Simonsen L, Tashiro M. The Japanese Experience with Vaccinating Schoolchildren against Influenza. N Engl J Med. 22 mars 2001;344(12):889-96.
10. Centers for Disease Control and Prevention (CDC). Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease--United States, 1998-2003. MMWR Morb Mortal Wkly Rep. 16 sept 2005;54(36):893-7.
11. Michel JP, Lang PO et Aspinall R. Integration of vaccinations of older adults in a life vcourse program. In: Oxford textbook of Geriatric Medicine. Oxford University Presss. Oxford; 2019. p. 681-7.
12. Andre FE, Booy R, Bock HL et al,. Vaccination greatly reduces disease, disability, death and inequity worldwide. Bull World Health Organ. 2008;140-6.
13. Jansen KU, Knirsch C, Anderson AS. The role of vaccines in preventing bacterial antimicrobial resistance. Nat Med. janv 2018;24(1):10-9.
14. Kingwell K. Vaccines take a shot at antimicrobial resistance. Nat Rev Drug Discov. avr 2018;17(4):229-31.
15. Modin D, Jørgensen ME, Gislason G, Jensen JS, Køber L, Claggett B, et al. Influenza Vaccine in Heart Failure. Circulation. 29 janv 2019;139(5):575-86.
16. Sung L-C, Chen C-I, Fang Y-A, Lai C-H, Hsu Y-P, Cheng T-H, et al. Influenza vaccination reduces hospitalization for acute coronary syndrome in elderly patients with chronic obstructive pulmonary disease: A population-based cohort study. Vaccine. juin 2014;32(30):3843-9.
17. Zangiabadian M, Nejadghaderi SA, Mirsaeidi M, Hajikhani B, Goudarzi M, Goudarzi H, et al. Protective effect of influenza vaccination on cardiovascular diseases: a systematic review and meta-analysis. Sci Rep. 26 nov 2020;10(1):20656.
18. Forbes HJ, Williamson E, Benjamin L, Breuer J, Brown MM, Langan SM, et al. Association of herpesviruses and stroke: Systematic review and meta-analysis. Nevels M, éditeur. PLoS ONE. 21 nov 2018;13(11):e0206163.
19. Verreault R, Laurin D, Lindsay J, De Serres G. Past exposure to vaccines and subsequent risk of Alzheimer's disease. CMAJ. 27 nov 2001;165(11):1495-8.
20. Christian Schnier, Janet Janbek, Richard Lathe, Jürgen Haas. Reduced dementia incidence following varicella zoster vaccination in Wales 2013–2020. medRxiv. July 25, 2021; doi: https://doi.org/10.1101/2021.07.22.21260981
21. Klinger D, Hill BL, Barda N, Halperin E, Gofrit ON, Greenblatt CL, Rappoport N, Linial M, Bercovier H. Bladder Cancer Immunotherapy by BCG Is Associated with a Significantly Reduced Risk of Alzheimer's Disease and Parkinson's Disease. Vaccines (Basel). 2021 May 11;9(5):491
22. Sochocka M, Zwolińska K, Leszek J. The Infectious Etiology of Alzheimer's Disease. CN [Internet]. 28 août 2017 [cité 13 sept 2020];15(7). Disponible sur: http://www.eurekaselect.com/150846/article
23. European Centre for Disease Prevention and Control,. Seasonal influenza vaccination and antiviral use in EU/EEA Member States [Internet]. 2018 [cité 24 juin 2021]. Disponible sur: https://www.ecdc.europa.eu/sites/default/files/documents/seasonal-influenza-antiviral-use-2018.pdf
24. Blank PR, Schwenkglenks M, Szucs TD. Disparities in influenza vaccination coverage rates by target group in five European countries: trends over seven consecutive seasons. Infection. oct 2009;37(5):390-400.
25. Wilson RS, Yu L, Lamar M, Schneider JA, Boyle PA, Bennett DA. Education and cognitive reserve in old age. Neurology. 05 2019;92(10):e1041-50.
26. Manca T. « One of the greatest medical success stories: » Physicians and nurses' small stories about vaccine knowledge and anxieties. Soc Sci Med. 2018;182-9.

27. Sturgis P, Brunton-Smith I, Jackson J. Trust in science, social consensus and vaccine confidence. Nat Hum Behav [Internet]. 17 mai 2021 [cité 21 juin 2021]; Disponible sur: http://www.nature.com/articles/s41562-021-01115-7
28. Corace K, Prematunge C, McCarthy A, Nair RC, Roth V, Hayes T, et al. Predicting influenza vaccination uptake among health care workers: what are the key motivators? Am J Infect Control. août 2013;41(8):679-84.
29. Larson H. Stuck: how vaccine rumors start - and why they don't go away. New York, NY: Oxford University Press; 2020. 1 p.
30. Federation of European Academies of Medicine. Vaccination in Europe – A joint FEAM/EASAC Commentary on the European Commission Roadmap on Strengthened cooperation against vaccine preventable diseases [Internet]. Disponible sur: https://www.feam.eu/vaccination-in-europe/
31. Michel J-P, Chidiac C, Grubeck-Loebenstein B, Johnson RW, Lambert PH, Maggi S, et al. Advocating vaccination of adults aged 60 years and older in Western Europe: statement by the Joint Vaccine Working Group of the European Union Geriatric Medicine Society and the International Association of Gerontology and Geriatrics-European Region. Rejuvenation Res. avr 2009;12(2):127-35.
32. 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. 2 juill 2016;12(7):1777-94.
33. Hotez PJ, Narayan KMV. Restoring Vaccine Diplomacy. JAMA. 15 juin 2021;325(23):2337-8.
34. The Lancet null. Global governance for COVID-19 vaccines. Lancet. 20 juin 2020;395(10241):1883.

Chapter 1

European schedule for vaccination in old people

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Vaccination against infectious diseases has saved millions of lives, providing great benefit for citizens and the whole society. Large epidemics of measles, mumps, rubella, pertussis, and hepatitis A occurred in Europe in the past decade and with efficient vaccination schedules been eliminated [1,2]. While all European countries implemented routine vaccination programmes for children, there are gaps in Europe for the use of vaccines designed for the old population [3]. Analysis conducted on vaccination coverages among adults in the EU, revealed an irregular distribution across countries with significant variations in terms of vaccine components, target groups, and the regulatory frame of implementation [1,4]. For clarification, no agreement has been found for old age definition across Europe.

Vaccination programmes for adults have the goal of providing protection against increased morbidity and mortality caused by vaccine preventable diseases during adulthood, age-related dysfunction, immunosenescence and co-morbidities associated with ageing [5]. Among the major challenges in immunisation policies, vaccine hesitancy is still recognized to be one of the ten threats for the global health, as stated by the World Health Organization in 2019 [6]. Beside this issue, also the large influx of migrants and refugees, the limited access to vaccine services and the lack of development of new vaccines, contributed to the rise of new epidemics of infectious diseases in recent years [7,8].

In April 2018, the European Commission adopted a proposal for a Council Recommendation and a roadmap on '*Strengthened Co-operation against Vaccine Preventable Diseases*'. A response to this proposal was prepared by the Federation of European Academies of Medicine (FEAM) in joint collaboration with the European Academies Science Advisory Council (EASAC), by publishing a commentary that addresses important issues, such as the need to develop strategies that enhance vaccine uptake in vaccine hesitant and vaccine resistant individuals, to implement a monitoring system for vaccine shortage, to stimulate vaccine production by industry at European level ensuring safety and quality of manufacturing, and to optimise schedules for those vaccines for which there is a shortage [9].

Following those initiatives and the COVID-19 pandemic, the current report suggests recommendations to harmonise vaccination schedules in Europe for the old population. In order to propose a comprehensive review, FEAM has launched in April 2021 a survey to its Academy network to obtain details of current vaccination schedules for old people available in different European countries. The survey included the following questions:

1. *What vaccines are available for the older population in your country and what are the age qualifications to receive those vaccines?*
2. *Is there a formal schedule for the administration of those vaccines in the older population?*
3. *At your country level, do you benefit of a national vaccine register? Do you have a national vaccine adverse event register?*
4. *In your country, which are the main limitations of vaccine uptakes by the old population? (Multiple choice)*
5. *Do you think there should be a formal schedule for adult vaccinations in your country?*
6. *Do you think that EU vaccine recommendations for the older population would increase vaccine prescriptions and uptakes?*
7. *Do you think that vaccine education of medical and healthcare professionals is enough developed in your country?*
8. *Any other comment or suggestion?*

Responses from different countries in Europe have been collected: Belgium, the Netherlands, Austria, Greece, Serbia, France, Spain, Lithuania, Switzerland, Germany, Israel, Portugal. The overall feedback clearly reflects the same data that the European Centre for Disease Prevention and Control (ECDC) recently published, revealing that all these European countries already implemented national vaccination schedules for adults (Table 1). However, this analysis also confirmed the existence of significant variations between individual countries in terms of target groups, vaccine components and regulatory frame of implementation, as confirmed by previous studies [1,4]. All European countries have influenza vaccination policies for high-risk groups, including older adults. This is probably attributed to the European Council recommendation on seasonal influenza vaccination published in 2009 aiming to improve vaccine uptake in older age and high-risk groups [10]. Beside the immunisation programmes for influenza, most European countries also have policies in place against herpes zoster (shingles), diphtheria, tetanus and pneumococcal infections.

A formal schedule for vaccine administration already exists for the older population in most of the countries (Table 1). However, there are considerable differences between EU member states. Furthermore, a general agreement on the importance of having such formal schedules was highlighted. Very few countries also have the benefit of a national vaccine register. Data on vaccination coverage is usually recorded in decentralised platforms or at regional level. The EudraVigilance register – operated by the European Medicines Agency (EMA) – provides data from across Europe, on suspected adverse events reported for drugs, including vaccines, stratified by age, sex, geographic location, and even the origin of their report. According to their principle of transparency, they point out that are raw data without any evaluation [11]. In addition to the EudraVigilance data collecting system, the EMA publishes a monthly overview, listing all safety signals discussed during the latest Pharmacovigilance Risk Assessment Committee (PRAC) meeting and the recommendations given for each of them. This overview includes PRAC recommendations for centrally and nationally authorized medicines [12]. This data promotes high quality evidence and are essential for the understanding of each vaccine safety. However, the lack of an equivalent efficacy European registry can lead to imbalanced interpretations and assumptions concerning vaccines, favouring the discrediting of their importance in our society.

Most countries interviewed were in favour of EU vaccine recommendations for the older population, as this initiative would increase vaccine uptake and therefore afford cost-effective protection to the older population. The main issues identified, which limit vaccine uptake, include lack of population knowledge, lack of confidence in vaccine safety, not enough integration of vaccine programmes in the primary healthcare systems and not enough presentation of a “life course immunisation programme”. Education plans for medical and healthcare professionals are also in place in many European countries, but mostly for a few specialties only. This still leaves margin for improvement and implementation of more extensive education programmes.

Vaccines for COVID-19

Contrary to policy schedules of the most common vaccines in use, results from the survey showed that vaccination programmes against COVID-19 are instead mostly homogeneous across Europe. The following countries have responded to the survey: Belgium, Spain, the Netherlands, Austria, Switzerland, Greece, Serbia, Portugal. From the data collected, the use of AstraZeneca, Pfizer/BioNTech, Moderna and Johnson & Johnson vaccines were implemented, with the exception of the Sputnik V and SinoPharm vaccines used in Serbia, alongside with Pfizer/BioNTech and AstraZeneca. Formal schedules for the administration of those vaccines were well implemented in each country, with data recorded in National Vaccine registers, with exception of Switzerland. All countries interviewed were in favour of EU vaccine recommendations for the older population, with only a few exceptions in support of policy recommendations implemented at national level as effectively as possible. Education programmes for vaccines against COVID-19 were also sufficiently developed for medical and healthcare professionals.

During the COVID-19 pandemic, many healthcare functions were severely disrupted. This resulted in reduced levels of routine vaccinations particularly for the younger age groups. For example, there are reports of HPV vaccination being severely disrupted.

Final comments

Additional comments received by FEAM Academies highlighted the potential need for compulsory vaccination that becomes necessary when vaccine recommendations do not reach their goal. However, compulsory vaccination is a highly contentious proposition and there are many objections, both legal and ethical. Lack of consensus for some immunization schedules was another important issue raised, as this might lead to reduced confidence in the entire adult vaccination programme. Moreover, great attention should be dedicated to accurate communication on adverse events. The COVID-19 pandemic clearly showed that information on side effects was used to change policy and create anxiety. Another major issue was also referring to the propagation of fake news online. The overall study revealed that most of interviewing Academies had comprehensive adult vaccination schedules with significant differences in vaccination policies between countries, mainly in terms of age qualification, vaccine components and frame of implementation. Particularly, the data collected raised concerns on the need for the society to be aware of the importance of vaccination, by improving communication of relevant information and implementing health education for both the general population and healthcare professionals as a basic tool to develop healthy lifestyle habits. Infectious diseases are a major cause of morbidity and mortality across the globe, mainly in older people and individuals with chronic diseases. Consequently, a greater education may contribute to higher acceptance and recognition of vaccine's benefits and is key to promote the establishment of more inclusive societies that allay fears and address concerns around vaccination efficacy. Our goal is thus to contribute to the establishment of a common immunisation program across Europe. Some differences might also be explained by cost issues, capacities for vaccine reimbursement, different criteria for the introduction of vaccines in national programmes, lack of licensed vaccines and differences in the logistics. However, such issues have not been addressed by the current study. Considering that elderly individuals are more inclined to contract severe infections and less responsive to vaccination, due to immunosenescence and preexisting inflammatory conditions, research to deepen our knowledge on the role of inflammation in vaccination responsiveness should remain of high priority to support the development of vaccination strategies tailored for the old population. There is still the need to identify new formulations that better stimulate the elderly immune system (see Chapters 3 and 5). In addition, the specific history of each individual is another component that should be considered as this causes large variation across the old population. Data from individual health history, integrated with clinical and immunological parameters, have the potential to

contribute to the identification of new markers that might lead to the development of vaccines specifically designed for the old population [13].

Country	Diphteria	Tetanus	Pertussis (acp)	PCV	PPSV23	TBE	IIV	Zoster	IPV	Measles	Total
Austria	■	■	■	■	■	■	■				7
Belgium	■	■	■	■	■		■				6
Bulgaria	■	■		■	■		■				5
Croatia							■				1
Cyprus					■		■				2
Czech Rep		■	■	■	■	■	■	■			7
Denmark					■		■				2
Estonia				■	■		■	■			4
Finland							■				1
France	■	■					■	■	■		5
Germany	■	■	■		■					■	5
Greece	■	■	■	■	■		■	■	■		8
Hungary				■	■		■				3
Ireland					■		■				2
Italy	■	■	■	■	■		■	■			7
Latvia	■	■					■				3
Lithuania							■				1
Luxembourg				■	■		■				3
Malta							■				1
The Netherlands					■		■				2
Poland				■			■				2
Portugal	■	■					■				3
Romania							■				1
Slovakia	■	■		■			■				4
Slovenia	■	■		■	■		■				5
Spain	■	■			■		■				4
Sweden					■						1
Norway					■		■				2
Liechenstein	■	■					■				3
Total	13	14	6	12	18	2	27	5	2	1	

PCV: Pneumococcal conjugate vaccine / PPSV23: Pneumococcal Polysaccharide Vaccine / TBE: Tick-borne encephalitis / IIV: Inactivated influenza vaccines / IPV: Inactivated polio vaccine

Table 1. Routine vaccination schedules recommended in European countries for the old population (>=65). Adaptation of the Table published on the ECDC website: https://vaccine-schedule.ecdc.europa.eu/

References

1. Piot, P., Larson, H.J., O'Brien, K.L., N'kengasong, J., Ng, E., Sow, S. and Kampmann, B., 2019. Immunization: vital progress, unfinished agenda. Nature, 575(7781), pp.119-129.
2. Maarten van Wijhe, Scott A McDonald, Hester E de Melker, Maarten J Postma, Jacco Wallinga. Effect of vaccination programmes on mortality burden among children and young adults in the Netherlands during the 20th century: a historical analysis. Lancet Infect Dis. 2016 May;16(5):592-598
3. Sheikh, S., Biundo, E., Courcier, S., Damm, O., Launay, O., Maes, E., ... & Postma, M. (2018). A report on the status of vaccination in Europe. Vaccine, 36(33), 4979-4992.
4. Cassimos, D. C., Effraimidou, E., Medic, S., Konstantinidis, T., Theodoridou, M., & Maltezou, H. C. (2020). Vaccination Programs for Adults in Europe, 2019. Vaccines, 2020 Jan 20;8(1):34.
5. Incalzi, R. A., Bernabei, R., Bonanni, P., Conversano, M., Ecarnot, F., Gabutti, G., ... & Sandri, F. (2020). Vaccines in older age: moving from current practice to optimal coverage—a multidisciplinary consensus conference. Aging Clinical and Experimental Research. 2020 Aug;32(8):1405-1415
6. World Health Organization. Top Ten Threats to Global Health. Available online: https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019
7. Ravensbergen, S.J.; Nellums, L.B.; Hargreaves, S.; Stienstra, Y.; Friedland, J.S. ESGITMWorking Group on Vaccination in Migrants. National approaches to the vaccination of recently arrived migrants in Europe: A comparative policy analysis across 32 European countries. Travel Med. Infect. Dis. 2019, 27, 33–38.
8. Andrew, M.K.; Bowles, S.K.; Pawelec, G.; Haynes, L.; Kuchel, G.A.; McNeil, S.A.; McElhaney, J.E. Influenza vaccination in older adults: Recent innovations and practical applications. Drugs Aging 2019 Jan;36(1):29-37.
9. See FEAM/EASAC joint commentary on Vaccination in Europe: An EASAC and FEAM commentary on the EC Roadmap 'Strengthened cooperation against vaccine preventable diseases' (2018): https://www.feam.eu/wp-content/uploads/EASAC-FEAM-Statement-on-vaccines-April-2018-FINAL.pdf
10. Implementation of the Council Recommendation of 22 December 2009 on Seasonal Influenza Vaccination (2009/1019/EU). Available online: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:348:0071:0072:EN:PDF
11. EudraVigilance – European Database of suspected adverse drug reaction reports. Available online: www.adrreports.eu
12. European Medicines Agency – Pharmacovigilance Risk Assessment Committee. Available online: www.ema.europa.eu/en/committees/pharmacovigilance-risk-assessment-committee-prac
13. Annalisa Ciabattini, Christine Nardini, Francesco Santoro, Paolo Garagnani, Claudio Franceschi, Donata Medaglini. Vaccination in the elderly: The challenge of immune changes with aging. Semin Immunol, 2018 Dec; 40:83-94. doi: 10.1016/j.smim.2018.10.010.

Chapter 2

The Ageing immune system – Implications for Vaccination

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Immune ageing in the context of immune physiology

In order to address how immune function changes with age, we must first consider the inherent time-dependency of normal immune responses. In a typical adaptive ("memory") response, an infective stimulus or vaccine triggers a highly structured sequence of time-dependent events. First, specific naïve cells are selected from a diverse pool of relatively inactive cells and recruited as effector cells. Their role is both to eliminate the current threat and subsequently to form a population of "memory cells" which are primed to make faster and more potent responses to subsequent rechallenge with an identical or similar pathogen. This paradigm applies to both T and B cells. Broadly speaking, T cells are responsible for cell-to-cell defences whilst B cells produce antibodies. B cells have an additional developmental step - they differentiate into bone-marrow resident plasma cells, the source of most circulating antibodies. Once the immediate challenge has passed, memory T cells recirculate between blood, tissues, lymph, and lymphoid organs. Some cells localise within bone-marrow in a resting (G_0) state [1] whilst others localise to tissues such as respiratory and gastrointestinal mucosa and skin where they constitute the "tissue-resident memory" (T_{RM}) population of T cells, providing a front-line of immune defence at likely sites of invasive infection. Memory cells are highly specific for the pathogen or vaccine from which they were primed; diversity is conferred by selecting and maintaining a very broad repertoire of T and B cell clones.

Maintaining such a very large spectrum of highly specific circulating cells in a state of readiness for decades is achieved primarily by maintaining clones, rather than keeping individual cells alive, as the progeny of homeostatic clonal proliferation share the antigen-specificity of their antecedent cells. By contrast, the survival of T_{RM} and bone-marrow plasma cells may be more dependent on cellular longevity [2]. This long-term clonal preservation is mediated through both the inherent properties of the immune cells themselves and through external survival signals. Re-exposure, or re-vaccination, will prompt expansion of already-selected infection-specific clones together with the recruitment of new naïve clones conferring longevity on the protective immune response. Interestingly, clonal lifespan appears to vary according to the stimulus. Yellow-fever vaccination, for example, induces very well-maintained, life-long protection [3], mediated by quiescent CD8+ T cells with epigenetic characteristics of effector cells [4]. Conversely, immunity for some other infections/vaccinations, such as coronaviruses, fades more rapidly [5]. SARS-CoV-2 (COVID-19) immunity specifically, appears to wane over a period of less than a year, at least in some people [6]. This fading response likely corresponds to a reduction in the population of clones specific for these pathogens.

Life-stage related changes in immune cell populations and immune function

Such normal time-dependent processes for immune memory are superimposed on changes related to the individual's life-stage. Although humans are born with a well-established adaptive immune system, new naïve cells continue to be added to the circulating pool throughout childhood and early adult life through the activity of the thymus gland. Thymic function peaks at puberty and declines progressively thereafter, although some continued activity may continue for decades; indeed, lymphocytes that have recently left the thymus can still be detected in blood well into old age [7]. With increasing thymic involution, maintenance of the naïve T-cell pool becomes increasingly dependent upon homeostatic proliferation of previously generated naïve cells [8]. The consequence is a loss in repertoire diversity of about 2- to 5-fold [8]. The actual size of the CD4+ T-cell pool, however, is surprisingly well maintained. This occurs via a combination of cellular longevity (naïve cells may live for years without dying or dividing) [9], and ongoing homeostatic proliferation (proliferation rates for both CD4+ and CD8+ naïve T cells are maintained into old age) [10]. This combination compensates well for the reduction in new thymic emigrants during ageing for CD4+ T cells but not for CD8+ cells. The size of the naïve CD8+ T-cell compartment is reduced significantly in old age in association with an increased clonality [8], which may be partly driven by cytomegalovirus (CMV) infection (see below.) The result is fewer CD8+ T cells, with a more limited range of specificities. In addition to such global changes in naïve/memory differentiation, more subtle changes in subset distribution also have functional impacts; for example, aberrant T helper subset differentiation and an increased proportion of regulatory T cells [11,12] both tend to suppress overall immune function. These changes are summarised in Figure 1.

For B cells, lymphopoietic precursors also become functionally less active in older people [13] resulting in a similar decline in naïve cell output. Although naïve B cells also have a long lifespan [14], they are progressively lost over time resulting in a loss of immune repertoire. In addition, reduced class-switch recombination and somatic hypermutation of immunoglobulin genes contribute to reduced antibody production and function (Figure 1) [15] whilst an attrition in the number of plasma cells in bone-marrow correlates with reduced antibody concentrations in blood [16]. Changes in total immunoglobulin levels with ageing vary according to class: a recent meta-analysis showed that IgA tends to be increased, IgG unchanged and IgM reduced in older people [17,18], although some studies have found increased IgG levels with increasing age.

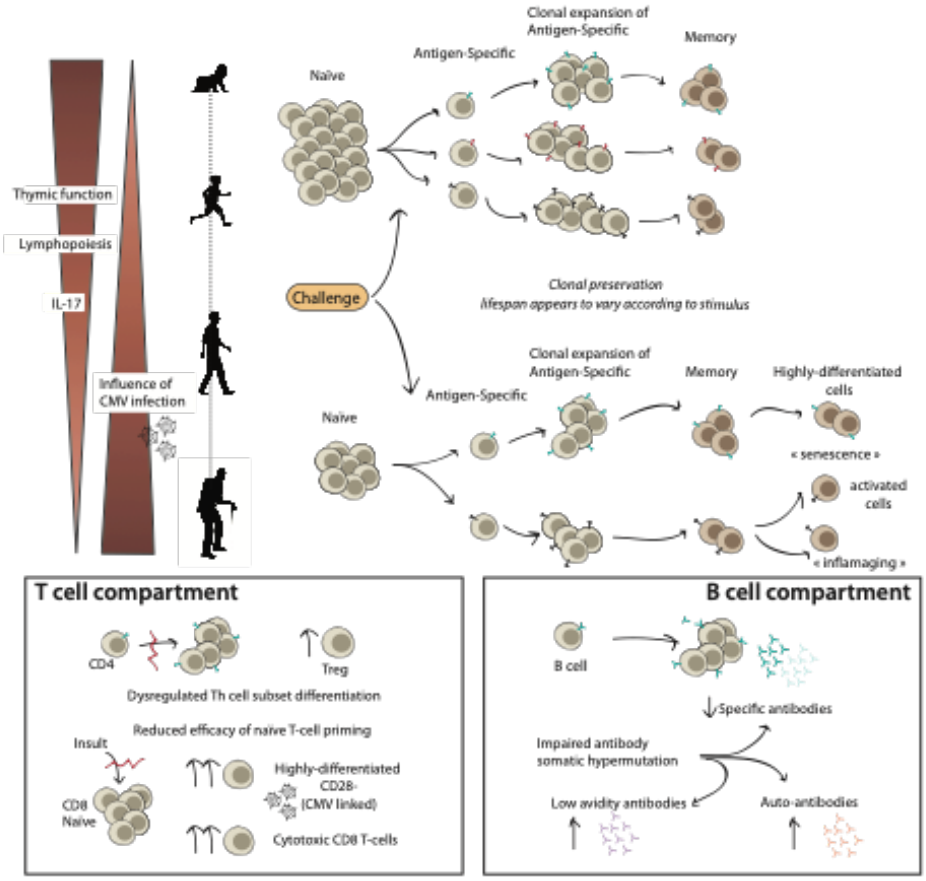

Figure 1. This figure illustrates the main changes in the adaptive immune system that have been reported to occur during aging (courtesy of Dr Ester Gea-Mallorqui, Oxford University).

Immune ageing in its anatomic context

Immune cells do not operate in a vacuum - the anatomical context of their activity is also important and changes with age. Microanatomical changes, such as the progressive replacement of haematopoietic and thymic tissue with adipose tissue seen with ageing, will likely impair not just the production and maintenance of T- and B-cell populations but also the survival of long-lived plasma cells by compromising stromal support for cell survival and proliferation. The response to ageing varies between tissues. One recent survey, including cells from eight different tissues, as well as blood, showed that the mechanisms for CD4+ and CD8+ T-cell homeostasis with ageing are tissue-dependent and that CD4+ and CD8+ T-cells have distinct age-related patterns of circulation and compartmentalization; importantly, T-cell composition at mucosal sites was found to be more stable than that in lymphoid tissues (Figure 1) [19]. Such observations could have implications for the types of vaccines and routes of delivery that may be more effective in the old population (see Chapter 3).

Immune pathology with ageing

The changes highlighted above might be considered normal time-dependent processes, rather than pathological, processes. Taken together, they do however mean that the functional capacity of the immune system to combat both new and previously encountered pathogens may become more limited over time with age. Superimposed upon these age-related changes are several processes which might be

considered pathological; here we focus on four such pathological changes: (i) increased inflammation – "inflamm-aging"; (ii) pathogen-driven effects, specifically the effects of CMV infection; (iii) cell senescence; and (iv) metabolic effects.

(i) Innate immune responses and "Inflamm-aging"

The term "Inflamm-aging" refers to a process of chronic sterile systemic low-grade inflammation thought to promote the development of age-related diseases [20]. It is believed to be driven either by a number of stimuli (including exposure to pathogens, cellular debris and components of the gut microbiome) or loss of control mechanisms (such as autophagy, or initiation of clonal haematopoiesis), and is associated with elevated plasma inflammatory markers. The primary underlying mechanism has been attributed to an overabundance of reactive oxygen species (ROS) released from malfunctioning mitochondria within the cell, leading to damaging oxidation of cellular components and activation of inflammatory cell death pathways such as necroptosis, although the processes involved in "Inflamm-aging" are clearly multiple and complex. Indeed, ROS can be anti-inflammatory in some contexts and anti-oxidant trials have yielded variable results [21].

(ii) Pathogen driven effects, specifically the effects of Cytomegalovirus (CMV) infection

Whilst the great majority of the older population have reduced numbers of circulating naïve CD8+ T-cells, some older people also possess substantial expansions of memory CD8+ T-cells which express "senescence" markers such as CD57 and shortened telomeres [22] (although expression of CD57 *per se* does not denote replicative senescence [23]). This group of individuals shows serological evidence of infection with the persistent herpes virus, cytomegalovirus. The contribution of CMV infection to immune ageing is controversial [24] and has been the subject of several international workshops [25], so cannot be dissected in detail here: further information can be found in a recent systematic review [26] and in Chapter 3.

Nevertheless, several epidemiological studies have reported associations between CMV seropositivity and increased mortality (particularly from cardiovascular disease and cancer) [27-29], with the highest levels of CMV antibody being linked with frailty [30]. Elevated CMV antibody levels are thought to reflect intermittent reactivation of viral replication, but whether CMV reactivation drives immune senescence or is a consequence of failing adaptive immune responses has not yet been fully resolved.

(iii) Cell senescence

All cells have mechanisms to limit their proliferation and protect themselves from DNA damage – probably as a defence mechanism against persistence of damaged cells and oncogenesis (development of malignancies). These mechanisms may limit the extent to which lymphocyte populations can expand over the long term. "Immunosenescence" is the term used to describe a stage of advanced cell differentiation which is associated with reduced function and limited capacity for proliferation [31]. The term is often used interchangeably with "T cell exhaustion" and the definition of both has been the subject of much debate [32,33]. Both can be defined in terms of function, proliferation, surface receptor expression and gene expression. Certainly, with ageing, more circulating cells show features of "senescence" and/or "exhaustion". It is often assumed that this limits functionality of the system, but it may represent a protective mechanism, ensuring that T cell clones required for immunosurveillance are retained into old age and not lost via elimination at the Hayflick limit [33]. Immunosenescence is a potential area for therapeutics [34]. Potential approaches include: firstly, removal of senescent cells, which appears to improve the function of remaining cells [35]; secondly, agents which inhibit implicated pathways such as p38 MAPkinase [36] may reverse age-related deficits in local immunity [37]. This raises the possibility that short-term administration of a senescence-reversing agent with vaccination would improve vaccine efficacy in the old population.

(iv) Metabolic effects of ageing

Cellular metabolic changes such as mitochondrial dysfunction are likely to contribute to reduced immune responses in the older population. Epigenetic changes are also important factors in determining the responsiveness of lymphocyte populations to stimulation and hence to vaccine responsiveness [38, 39]. Moreover, micronutrient changes, such as Vitamin D deficiency, also contribute; a recent study in deficient older adults showed that Vitamin D replacement led to restoration of adaptive immune responses to Varicella Zoster virus in the skin [40]. These important examples illustrate the impact that metabolic changes may have; further discussion is beyond the scope of this review.

In addition to the above specific pathological processes, comorbidities more common in the older population, such as diabetes, cardiovascular disease, and compromised tissue integrity, also contribute to susceptibility to infection and impaired vaccine responses. These are addressed in Chapter 3.

Evidence for loss of immune function with age

The above review of physiological and pathological processes leads one to the conclusion that older people generally have reduced immune function compared to younger people. In contrast with this generalised conclusion, it is clear that some very old individuals have excellent immune function whereas other relatively young individuals have parameters and responses one would expect from a very "old" immune system. The relationship of immunity with frailty is discussed elsewhere in this report (see Chapter 3), but it is clear that chronological ageing and immune ageing, while often correlated, are not the same thing. That "ageing" of the immune system is clinically meaningful has been demonstrated in long-term prognostic studies such as the OCTO and NONA studies which have shown an association between immunological changes (specifically an inverted CD4/CD8 ratio and T-cell activation markers) and mortality [41,42]. Recently, multiple "omic" studies of samples collected longitudinally over 9 years from a cohort of >100 healthy adults were used to estimate immune age in what the authors refer to as a "clinically meaningful metric" (https://pubmed.ncbi.nlm.nih.gov/30842675/). The key components of this metric (represented as gene expression profiles) were evaluated in the Framingham heart study and demonstrated a significant correlation with cardiovascular disease: IMM-AGE calculated in this way was also strongly associated with mortality.

(i) Clinical evidence

There is a wealth of data supporting the concept that ageing results in increased susceptibility to infection. For example, influenza susceptibility and mortality appear much higher in people over 65 years of age [43]. Similarly, the incidence of and mortality from bacterial pneumonia are higher in older adults [44]. There are, of course, many non-immune factors contributing to this increased risk, such as reduced mobility, the presence of co-morbidities, healthcare-associated infection, and loss of barrier functions. Hence separating the relative contributions of aging per se and comorbidities is very difficult. Despite this uncertainty, the frequency of infections in the older population is generally considered indicative of at least a degree of reduced immune function.

(ii) Evidence from laboratory indices

Evidence to support the concept that infections in the older population are related to loss of immune function derive from a plethora of laboratory studies in humans and in animal models. A comprehensive review of immune abnormalities with ageing is beyond the scope of this review but they are briefly summarised in Figure 1. Many parameters have been measured in different studies and most show some evidence of decline with age. However, it is not simply the case that 'being older' equates to having less immune function – it is more a case that 'being older' results in more immune dysfunction. For example, older people are more likely to generate auto-antibodies against IFN-α and -ω but not -β, and this may contribute to their increased susceptibility to COVID-19 pneumonia [45]. Conversely, some parameters,

such as the size of the CD4 T cell pool (above) and the production of monocyte-derived cytokines and IL-17 do not appear to change significantly with age [46].

(iii) Evidence from vaccine responsiveness in the elderly

A more accurate measure of "real life" immune function is the ability of the immune system to generate adaptive responses to vaccine antigens administered in later life. Vaccines have been widely reported to lead to lower antibody titres and affinity in many older people: levels also decline more rapidly than would be the case in younger people [47,48]. Where measured, cellular responses are also reduced [47, 49]. This aspect is dealt with more fully in Chapter 4.

Caveats and difficulties

It is worth drawing attention to a number of caveats and difficulties in this area. Firstly, this discussion has focused on the adaptive immune system as this is most relevant to vaccine strategies in the older population, but major changes in innate immunity also occur with ageing. Secondly, many of the paradigms or supposed 'truths' about immunosenescence derive from recapitulation of previous citations, many of which are opinions or reviews, rather than being based on analysis of original observations or data. This seems to be particularly problematic for "inflammaging", where reviews dominate the published literature. In terms of experimental data, our paradigms are based on both human and animal data. Observations in animals however, particularly small animals, are difficult to extrapolate to humans; an "old" mouse is not the same as an old human. Small animal studies do, however, have an important role in hypothesis generation for human immunology and may often be the only route to mechanistic insights. In human studies, control populations may not be appropriate, limiting interpretation. Terminology is also problematic; there is considerable ambiguity in the way specific terms are used. "Immunosenescence" for example is used to refer to a variety of different processes. "Old age" is also defined in many different ways (discussed in the introductive chapter). There is also a great tendency to over-simplify and say, 'older equals less immunity'; the situation is far more complex; a concept that older equals 'more variable' and/or 'more dysregulated' would be closer to the truth; exaggerated immune responses are just as much a feature of ageing as impaired immune responses. There is also a huge difference between healthy and active older people, who basically have normal immune responses, and frail older people in whom immune defects occur. Finally, it is easy to neglect the complex interplay between different aspects of immune function – some of the "abnormalities" observed are compensatory mechanisms for changes elsewhere in the immune system or protective mechanisms designed for example to reduce the risk of oncogenic transformation.

Summary

Because immune responses are inherently time-dependent processes, immune function will inevitably change with ageing. Pathological processes are superimposed on this chronological framework. Reversal or management of some of these processes may be possible and agents to reverse cellular senescence are being actively explored. The degree of immune impairment will vary between individuals of the same age and cannot currently be reliably predicted by any specific marker. The potential use of biomarkers of immune ageing is an active area for research and may yield diagnostics to guide vaccination strategies. At present, however, in the absence of the widespread use of immunosenescence-reversing agents and biomarkers, when considering vaccination strategies for the older population, it is reasonable to assume that the immune system will, on average, be less responsive in older than younger adults.

Approaches to accommodate this global deficit might include vaccines with stronger adjuvant activity, to overcome higher thresholds for activation, vaccines with different antigenic loads, and vaccines with

different delivery routes or dosing intervals. From the above discussion of immune physiology and pathology, it can be seen that approaches such as use of specific vaccine types, enhanced adjuvants or agents to promote vaccine responses, senescence reversal agents, merit further exploration and further research in this area should be encouraged.

References

1. Okhrimenko A, Grün JR, Westendorf K, Fang Z, Reinke S, von Roth P, Wassilew G, Kühl AA, Kudernatsch R, Demski S, Scheibenbogen C, Tokoyoda K, McGrath MA, Raftery MJ, Schönrich G, Serra A, Chang HD, Radbruch A, Dong J. Human memory T cells from the bone marrow are resting and maintain long-lasting systemic memory. Proc Natl Acad Sci U S A. 2014 Jun 24;111(25):9229-34. doi: 10.1073/pnas.1318731111. Epub 2014 Jun 10. PMID: 24927527; PMCID: PMC4078840
2. Cornelis R, Chang HD, Radbruch A. Keeping up with the stress of antibody production: BAFF and APRIL maintain memory plasma cells. Curr Opin Immunol. 2021 Aug;71:97-102. doi: 10.1016/j.coi.2021.06.012. Epub 2021 Jul 22. PMID: 34303157.
3. Wieten RW, Jonker EF, van Leeuwen EM, Remmerswaal EB, Ten Berge IJ, de Visser AW, et al. A Single 17D Yellow Fever Vaccination Provides Lifelong Immunity; Characterization of Yellow-Fever-Specific Neutralizing Antibody and T-Cell Responses after Vaccination. PLoS One. 2016;11(3):e0149871.
4. Akondy RS, Fitch M, Edupuganti S, Yang S, Kissick HT, Li KW, et al. Origin and differentiation of human memory CD8 T cells after vaccination. Nature. 2017;552(7685):362-7.
5. Huang AT, Garcia-Carreras B, Hitchings MDT, Yang B, Katzelnick LC, Rattigan SM, et al. A systematic review of antibody mediated immunity to coronaviruses: kinetics, correlates of protection, and association with severity. Nat Commun. 2020;11(1):4704.
6. Chia WN, Zhu F, Ong SWX, Young BE, Fong SW, Le Bert N, et al. Dynamics of SARS-CoV-2 neutralising antibody responses and duration of immunity: a longitudinal study. Lancet Microbe. 2021;2(6):e240-e9.
7. Douek DC, McFarland RD, Keiser PH, Gage EA, Massey JM, Haynes BF, et al. Changes in thymic function with age and during the treatment of HIV infection. Nature. 1998;396(6712):690-5.
8. Goronzy JJ, Fang F, Cavanagh MM, Qi Q, Weyand CM. Naive T cell maintenance and function in human aging. J Immunol. 2015;194(9):4073-80.
9. Wallace DL, Zhang Y, Ghattas H, Worth A, Irvine A, Bennett AR, et al. Direct measurement of T cell subset kinetics in vivo in elderly men and women. J Immunol. 2004;173(3):1787-94.
10. Westera L, van Hoeven V, Drylewicz J, Spierenburg G, van Velzen JF, de Boer RJ, et al. Lymphocyte maintenance during healthy aging requires no substantial alterations in cellular turnover. Aging Cell. 2015;14(2):219-27.
11. Moro-García MA, Alonso-Arias R, López-Larrea C. When Aging Reaches CD4+ T-Cells: Phenotypic and Functional Changes. Front Immunol. 2013 May 10;4:107. doi: 10.3389/fimmu.2013.00107
12. Lorenzo EC, Bartley JM, Haynes L. The impact of aging on CD4(+) T cell responses to influenza infection. Biogerontology. 2018 Dec;19(6):437-446. doi: 10.1007/s10522-018-9754-8
13. Ciabattini A, Nardini C, Santoro F, Garagnani P, Franceschi C, Medaglini D. Vaccination in the elderly: The challenge of immune changes with aging. Semin Immunol. 2018;40:83-94.
14. B-cell kinetics in humans: rapid turnover of peripheral blood memory cells. Macallan DC, Wallace DL, Zhang Y, Ghattas H, Asquith B, de Lara C, Worth A, Panayiotakopoulos G, Griffin GE, Tough DF, Beverley PC. Blood. 2005 May 1;105(9):3633-40. doi: 10.1182/blood-2004-09-3740. Epub 2005 Jan 11. PMID: 15644412
15. Bonnie B Blomberg, Daniela Frasca. Age effects on mouse and human B cells. Immunol Res. 2013 Dec;57(1-3):354-60. doi: 10.1007/s12026-013-8440-9
16. Pritz, T., Lair, J., Ban, M., Keller, M., Weinberger, B., Krismer, M. and Grubeck-Loebenstein, B. (2015), Plasma cell numbers decrease in bone marrow of old patients. Eur. J. Immunol., 45: 738-746. https://doi.org/10.1002/eji.201444878
17. Samer Raza Khan et al. Determinants and Reference Ranges of Serum Immunoglobulins in Middle-Aged and Elderly Individuals: a Population-Based Study J Clin Immunol. 2021 Sep 10. doi:

10.1007/s10875-021-01120-5. Online ahead of print. PMID: 34505230 DOI: 10.1007/s10875-021-01120-5
18. Determinants of Serum Immunoglobulin Levels: A Systematic Review and Meta-Analysis Front Immunol .2021 Apr 7;12:664526. doi: 10.3389/fimmu.2021.664526. eCollection 2021. PMID: 33897714 PMCID: PMC8058410 DOI: 10.3389/fimmu.2021.664526
19. Thome JJ, Yudanin N, Ohmura Y, Kubota M, Grinshpun B, Sathaliyawala T, et al. Spatial map of human T cell compartmentalization and maintenance over decades of life. Cell. 2014;159(4):814-28.
20. 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.
21. Tan BL, Norhaizan ME, Liew WP, Sulaiman Rahman H. Antioxidant and Oxidative Stress: A Mutual Interplay in Age-Related Diseases. Front Pharmacol. 2018 Oct 16;9:1162. doi: 10.3389/fphar.2018.01162. PMID: 30405405; PMCID: PMC6204759
22. Pawelec G. Immunosenenescence: role of cytomegalovirus. Exp Gerontol. 2014;54:1-5.
23. Raya Ahmed et al Cell Reports. 2020 Dec 15;33(11):108501. doi: 10.1016/j.celrep.2020.108501. CD57 + Memory T Cells Proliferate In Vivo PMID: 33326780 PMCID: PMC7758161 DOI: 10.1016/j.celrep.2020.108501
24. Sarah E. Jackson , George X. Sedikides, Georgina Okecha, Emma L. Poole, John H. Sinclair and Mark R. Wills. Latent Cytomegalovirus (CMV) Infection Does Not Detrimentally Alter T Cell Responses in the Healthy Old, But Increased Latent CMV Carriage Is Related to Expanded CMV-Specific T Cells. Published on 26 June 2017. Front. Immunol. doi: 10.3389/fimmu.2017.00733
25. Nikolich-Zugich J, van Lier RAW. Cytomegalovirus (CMV) research in immune senescence comes of age: overview of the 6th International Workshop on CMV and Immunosenescence. Geroscience. 2017;39(3):245-9.
26. Weltevrede M, Eilers R, de Melker HE, van Baarle D. Cytomegalovirus persistence and T-cell immunosenescence in people aged fifty and older: A systematic review. Exp Gerontol. 2016;77:87-95.
27. Simanek AM, Dowd JB, Pawelec G, Melzer D, Dutta A, Aiello AE. Seropositivity to cytomegalovirus, inflammation, all-cause and cardiovascular disease-related mortality in the United States. PLoS One. 2011;6(2):e16103.
28. Gkrania-Klotsas E, Langenberg C, Sharp SJ, Luben R, Khaw KT, Wareham NJ. Seropositivity and higher immunoglobulin g antibody levels against cytomegalovirus are associated with mortality in the population-based European prospective investigation of Cancer-Norfolk cohort. Clin Infect Dis. 2013;56(10):1421-7.
29. Savva GM, Pachnio A, Kaul B, Morgan K, Huppert FA, Brayne C, et al. Cytomegalovirus infection is associated with increased mortality in the older population. Aging Cell. 2013;12(3):381-7.
30. Wang GC, Kao WH, Murakami P, Xue QL, Chiou RB, Detrick B, et al. Cytomegalovirus infection and the risk of mortality and frailty in older women: a prospective observational cohort study. Am J Epidemiol. 2010;171(10):1144-52.
31. van Deursen, J. The role of senescent cells in ageing. Nature 509, 439–446 (2014). https://doi.org/10.1038/nature13193
32. Blank CU, Haining WN, Held W, Hogan PG, Kallies A, Lugli E, Lynn RC, Philip M, Rao A, Restifo NP, Schietinger A, Schumacher TN, Schwartzberg PL, Sharpe AH, Speiser DE, Wherry EJ, Youngblood BA, Zehn D. Defining 'T cell exhaustion". Nat Rev Immunol. 2019 Nov;19(11):665-674. doi: 10.1038/s41577-019-0221-9
33. Graham Pawelec. Is There a Positive Side to T Cell Exhaustion? Front. Immunol., 29 January 2019 | https://doi.org/10.3389/fimmu.2019.00111
34. Paez-Ribes M, González-Gualda E, Doherty GJ, Muñoz-Espín D. Targeting senescent cells in translational medicine. EMBO Mol Med. 2019 Dec;11(12):e10234. doi: 10.15252/emmm.201810234. Epub 2019 Nov 19. PMID: 31746100; PMCID: PMC6895604.
35. https://onlinelibrary.wiley.com/doi/10.1111/acel.12971- Palacio2019
36. Callender LA, Carroll EC, Beal RWJ, Chambers ES, Nourshargh S, Akbar AN, Henson SM. Human CD8(+) EMRA T cells display a senescence-associated secretory phenotype regulated by p38 MAPK. Aging Cell. 2018. 17(1)

37. Vukmanovic-Stejic M, Chambers ES, Farinas MS, Sandhu D, Fuentes-Duculan J, Patel N, Agius E, Lacy KE, Turner CT, Larbi A, Birault V, Noursadeghi M, Mabbott NA, Rustin MHA, Krueger J, Akbar AN. Enhancement of cutaneous immunity during ageing by blocking p38 MAPkinase induced inflammation. J Allergy Clin Immunol. 2017. pii: S0091-6749(17)31766-9
38. Miriam G. Jasiulionis - Abnormal Epigenetic Regulation of Immune System during Aging. Front. Immunol., 12 February 2018 | https://doi.org/10.3389/fimmu.2018.00197
39. Mihai G. Netea, Jorge Domínguez-Andrés, Luis B. Barreiro, Triantafyllos Chavakis, Maziar Divangahi, Elaine Fuchs, Leo A. B. Joosten, Jos W. M. van der Meer, Musa M. Mhlanga, Willem J. M. Mulder, Niels P. Riksen, Andreas Schlitzer, Joachim L. Schultze, Christine Stabell Benn, Joseph C. Sun, Ramnik J. Xavier & Eicke Latz. Defining trained immunity and its role in health and disease. Nature Reviews Immunology 20, pages 375–388 (2020)
40. Emma S. Chambers, Milica Vukmanovic-Stejic, Barbara B. Shih, Hugh Trahair, Priya Subramanian, Oliver P. Devine, James Glanville, Derek Gilroy, Malcolm H. A. Rustin, Tom C. Freeman, Neil A. Mabbott & Arne N. Akbar. Recruitment of inflammatory monocytes by senescent fibroblasts inhibits antigen-specific tissue immunity during human aging. Nature Aging volume 1, pages101–113 (2021)
41. Age-related change in peripheral blood T-lymphocyte subpopulations and cytomegalovirus infection in the very old: the Swedish longitudinal OCTO immune study. J Olsson 1 , A Wikby, B Johansson, S Löfgren, B O Nilsson, F G Ferguson. Mech Ageing Dev 2000 Dec 20;121(1-3):187-201. doi: 10.1016/s0047-6374(00)00210-4. PMID: 11164473 DOI: 10.1016/s0047-6374(00)00210-4
42. Wikby A., Strindhall J., Johansson B. (2009) The Immune Risk Profile and Associated Parameters in Late Life: Lessons from the OCTO and NONA Longitudinal Studies. In: Fulop T., Franceschi C., Hirokawa K., Pawelec G. (eds) Handbook on Immunosenescence. Springer, Dordrecht. https://doi.org/10.1007/978-1-4020-9063-9_1
43. Paget J, Spreeuwenberg P, Charu V, Taylor RJ, Iuliano AD, Bresee J, et al. Global mortality associated with seasonal influenza epidemics: New burden estimates and predictors from the GLaMOR Project. J Glob Health. 2019;9(2):020421.
44. Henig O, Kaye KS. Bacterial Pneumonia in Older Adults. Infect Dis Clin North Am. 2017;31(4):689-713.
45. Bastard P. et al Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths. Sci Immunol. 2021 Aug 19;6(62):eabl4340. doi: 10.1126/sciimmunol.abl4340. PMID: 34413139; PMCID: PMC8521484.
46. ter Horst et al. Host and Environmental Factors Influencing Individual Human Cytokine Responses. Cell 2016; 167:1111. DOI: 10.1016/j.cell.2016.10.018
47. Wagner A, Garner-Spitzer E, Jasinska J, Kollaritsch H, Stiasny K, Kundi M, et al. Age-related differences in humoral and cellular immune responses after primary immunisation: indications for stratified vaccination schedules. Sci Rep. 2018;8(1):9825.
48. Wagner A, Weinberger B. Vaccines to Prevent Infectious Diseases in the Older Population: Immunological Challenges and Future Perspectives. Front Immunol. 2020;11:717.
49. Weinberg A, Canniff J, Rouphael N, Mehta A, Mulligan M, Whitaker JA, et al. Varicella-Zoster Virus-Specific Cellular Immune Responses to the Live Attenuated Zoster Vaccine in Young and Older Adults. J Immunol. 2017;199(2):604-12.

Chapter 3

The effects of comorbidity on the vaccination response in aged people

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There is a general belief that responses to vaccinations, mainly assessed by measuring antibodies against vaccine antigens and protection against the infection targeted, are seriously impaired in ageing individuals. Recently, it has become clear in clinical studies in older people without comorbidities that the response is normal when vaccinated with potent new vaccines such as the one used against herpes zoster [1]. More recently the mRNA vaccines against SARS-CoV-2 have shown good responses in older people [2], although waning of the immune responses seem to be relatively rapid after a 2-dose regiment [3]. In this context, it should be noted that many of the vaccine studies performed in the ageing population have been done with the conventional influenza vaccines. Immune responses to influenza vaccines, especially those that do not contain a potent adjuvant, are variable and often not optimal.

In recent studies, it has been found that pre-vaccination influenza strain-specific antibody titres are a major determinant for the post-vaccination responses [4,5], and indeed have been used as a surrogate marker of protection. In line with this notion, it is not surprising that higher dosages and booster dosages of influenza vaccine are able to compensate to some extent for the moderate responses observed in elderly people [6]. These data with improved responses to higher vaccine dosages or boosters of influenza vaccine may suggest that similar approaches are rational for other vaccines as well.

An important advance is the development of high-dose Influenza vaccine (Fluzone HD influenza vaccine), in which the antigen dose has been quadrupled. Because of the favorable responses in aged people [7], many European countries recommend the use of this vaccine.

It is a common finding with many earlier vaccines that the serological response in old people is lower than in younger people. In a retrospective study investigating the role of age and sex on the response to hepatitis B vaccine in a healthy population, Vermeiren et al found that this age-dependent decline in vaccine responsiveness starts well before the age of 60 and is stronger in males than in females [8].

Ageing is often accompanied by chronic diseases and medication; these conditions may especially hamper vaccine responses and the resulting degree of protection. However, in many studies on vaccine responses in old people, the role of comorbidity and medication is not taken into account.

Older residents in long-term care facilities and frailty conditions

In a study performed in a nursing facility in the Netherlands, the antibody response to influenza was inversely related with the loss of activities of daily living [9]. In an earlier study, Gross et al had come to similar conclusions using the chronic health evaluation score [10]. The serological response to conventional hepatitis B vaccine has been found to be low and non-protective in approximately two thirds of the residents of a skilled nursing facility. The poor response in this study could not be accounted for by age, sex, ethnicity, body mass index, diabetes or smoking [11]. Based on these findings one might expect that frailty, the geriatric condition in which somatic and psychosocial stressors make the patient vulnerable to adverse health outcomes, would be a determinant for a poor vaccine response. Somewhat surprisingly however, frailty does not appear to affect the immune response to and protection by influenza vaccination [4,5]. Age as such was not a determinant of the response to influenza vaccine in frail old people [4]. It is important to note that frailty is not synonymous with multimorbidity.

Cytomegalovirus infection

Cytomegalovirus (CMV) is a ubiquitous herpesvirus that latently infects a large proportion of the population. Since the virus is known to affect the T-lymphocyte compartment of the human immune system, it has been speculated that it is a potential driver of immunosenescence and hence interferes with vaccine responses [12,13]. As noted in Chapter 2, there is quite some controversy on this issue in the literature. In a recent systematic review, it was concluded however that there is no proof of a negative effect of CMV infection on the antibody response to influenza vaccination [14].

Obesity

Recently, much attention has been given to obesity as a risk factor for a poor prognosis in patients with COVID-19. Similarly, obese individuals run a greater risk for a poor outcome with influenza. Few studies have been performed in obese subjects regarding their response to vaccination. In studies with influenza vaccines, the initial antibody response is high in obese individuals, but it wanes faster than in non-obese volunteers [15,16] and protection may be less [17]. Although there are many studies in obese mice which report a variety of immunological defects, the immunological mechanisms to explain greater susceptibility to infection in humans and the early waning of the human specific antibody response are scarce. The latter has been attributed to reduced CD8+ T cell activation 12 months post vaccination [18]. Finally, in obese individuals, the vaccine may be delivered in the fat instead of the muscle. Although this risk is probably lower with injections into the deltoid muscle than into the gluteal muscle [19], there is remarkably little attention to this issue in terms of assessing the magnitude of the vaccine response with intra-lipomatous vaccination.

Nutritional status

Protein-energy malnutrition and micronutrient malnutrition are not rare in aged people. The impact of these conditions on immune function has been studied already for decades, and a variety of abnormalities have been detected. For vaccine responses, the B- and T-cell function as well as monocyte/macrophage and dendritic cell function are crucial. Most studies on protein-energy malnutrition have been performed in children in low-income settings (for an excellent review see reference 19). In these studies, secretory IgA may be decreased but not until there is severe malnutrition, while circulating immunoglobulin concentrations are

remarkably normal. Most proinflammatory cytokines tends to be either in the normal range or decreased. T cell function has been reported to be decreased. In malnourished children the serological response to the various vaccines is in general pretty normal (although the quality and the duration of the response may be suboptimal); severe malnutrition is accompanied with decreased serological responses [20,21]. We cannot extrapolate these findings the aged population, so more research is needed here.

In micronutrient/vitamin deficiency, deficiency of vitamin D is of interest, especially since deficiency of vitamin D is associate with severe outcome of infections like COVID-19 [22], and many people at older age have a vitamin D deficiency [23]. However, vitamin D deficiency does not seem to diminish the serological response to influenza vaccine [24] and to COVID-19 mRNA vaccine [25]. Vitamin D suppletion does not affect the influenza vaccine response in aged people with vitamin D deficiency [26].

Deficiencies of micronutrients such as iron and perhaps zinc could also negatively affect the response to relevant vaccines [27].

Diabetes mellitus

Both type-1 and type-2 diabetes mellitus are important comorbidities in older individuals. Diabetic patients are more vulnerable to common infections such as mucocutaneous candidiasis, bacterial skin infections, urinary tract infections and pneumonia [28], tuberculosis, and rare infections such as infections caused by zygomycetes. Hence, many physicians consider these patients as immunocompromised, and a lot of studies have been performed showing a broad spectrum of immune abnormalities. Based on the latter, one might expect poor vaccine responses. However, from the available studies, a rather mixed picture emerges. In a post-hoc analysis of a large, controlled trial with pneumococcal conjugate vaccine in older patients, Huijts et al surprisingly found increased vaccine efficacy (>82%) in diabetic patients, both in patients with and without insulin [29]. There are a limited number of studies investigating vaccine response in diabetics exposed to conventional hepatitis B vaccine. In a large study in type-2 diabetic patients, a near normal response was found. Still, the sero-protection rate was lower in patients over 60 years of age (58.2%) than in those under 60 (>81%) [30]. Most studies with hepatitis B vaccine in type-1 diabetic patients were performed in children and adolescents. These studies met with variable results. As the response in children is outside the scope of this report, these will not be summarized here. Since diabetic patients are considered to be at greater risk for serious influenza, annual vaccination against seasonal influenza is generally recommended.

Although there is a lack of high quality randomized controlled clinical trials, systematic reviews conclude that influenza vaccination in diabetic patients is effective based on influenza morbidity and mortality as outcome parameters. Also, the antibody response against influenza was found to be normal in diabetic patients [31,32]. In many of the papers, patients with type-1 or type-2 diabetes are not separately assessed, and this should be the object of additional studies in the future.

Impaired kidney function and dialysis

In patients with chronic renal failure, T cell immunity is impaired. Hence the response to vaccines is considered to be suboptimal. The effectiveness of influenza vaccine and of pneumococcal vaccine is impaired but may be linked more to proteinuria than to renal function per se [33]. It is well documented that patients on hemodialysis have an impaired response to vaccination, especially to hepatitis B vaccines. Diabetes in these patients has been reported to further impair responses [34]. Several strategies have been investigated in dialysis patients to enhance the response. Strategies that have been tried include using higher antigen

doses, intradermal administration [35], repeated vaccinations, coadministration of other vaccines [34], and coadministration of immunostimulants like interleukin-2 [36], and better adjuvants (see below). Improved responses have been achieved, indeed, with intradermal administration of hepatitis B vaccines, but the best vaccine, the optimal dose, number of doses administered, and frequency of administration have not yet been established [37]. In a recent trial in healthy non-responders to conventional hepatitis B vaccine, two additional vaccines were investigated: one with a higher antigenic dose (HBVaxPro-40) and one with a potent lipid-based adjuvant AS04 (monophosphoryl lipid A). Revaccination with the latter two vaccines resulted in significantly higher antibody titres [38]. The proportion of responders was higher with the AS04. Because of the better response, the latter vaccine is currently registered for hemodialysis patients. Vaccination with an mRNA vaccine against COVID-19 also resulted in suboptimal responses in kidney transplant recipients and dialysis patients [39].

Immunomodulating treatment

The number of immunomodulatory drugs available has greatly increased over the past decades. Also, their potency to modulate the immune system is much greater than in the past. As these drugs are aimed at suppressing the immune response, effects on vaccine responses are to be expected. Some drugs have a profound effect on B lymphocytes (e.g., the anti-CD20 monoclonal antibody Rituximab) whereas others mainly affect T lymphocytes (e.g., cyclosporin) and still others have effects on both T and B cells (e.g., cyclophosphamide). In practice, patients will receive combinations of drugs, the effects of which on vaccine responses are unknown. One major problem is that clinical studies that investigate vaccine responses under immunosuppressive treatment are very heterogeneous in terms of the size of the study, of the drugs used (including duration and dose), the underlying diseases of the patients, the vaccine studied, and the assessment of the vaccine response. Most often the effect of ageing is not reported. A good example of the kind of studies needed is a recent meta-analysis of hepatitis A vaccine in patients on immunosuppressive drugs [40]. This vaccine, which is mainly used for travelers, has a seroconversion rate up to 100% after the second dose in healthy people. In patients on immunosuppression the serological response rate is highly variable, ranging from 0 to 97% after the second vaccination. TNF-alpha inhibitors in monotherapy seem to interfere less strongly than conventional immunosuppressive drugs (such as methotrexate, azathioprine and cyclosporin). The latter effect of TNF-alpha inhibitors was also found in a meta-analysis in which the effects of immunosuppressive drugs on the serological response to pneumococcal vaccines were assessed [41]. Interestingly, the response to the T-cell dependent pneumococcal conjugate vaccine was more impaired than of the T-cell-independent pneumococcal polysaccharide vaccine.

The most commonly prescribed immunosuppressive drugs in older patients are glucocorticosteroids. In seven large cohort studies in patients (42500 individuals) aged 55-80 years old, 2.2 to 9.2% used corticosteroids [42]. Corticosteroids have a wide range of (largely immunosuppressive) effects on the immune system. Effects on phagocytic cells, cytokine production and T cells, and to a lesser extent on B cells may affect vaccine responses. Few studies have been done on vaccine responses with corticosteroids as the single treatment, and it is often difficult to discern the independent effect of the underlying illness (e.g., SLE). In a review on influenza vaccination, the effects were found to be controversial, ranging from a normal serological response to impaired responses [43].

Conclusions

It is clear from the above that the suboptimal vaccine responses that occur in old patients may be due to ageing of the immune system or be due to underlying illnesses and their treatment. This implies that if protection by a vaccine is really needed, the serological response should be checked. It should be stressed however that measuring antibody response is only a partial answer: specific T-cell responses may also contribute to protection, but there is little information available in the literature about cellular immunity

induced by vaccines. A highly relevant question is whether we can optimize the vaccination response in older individuals with or without comorbidities. As discussed in this chapter, the effects of ageing may be overcome with 'better' vaccines. For instance, vaccines with the AS04 adjuvant perform better in ageing patients. Likewise, the mRNA vaccines seem to be less vulnerable to ageing effects. As already alluded above, additional strategies include higher antigen dose, intradermal administration, repeated vaccination, sequential administration of different kind of vaccines against the same pathogen, coadministration of other vaccines, and coadministration of immunostimulants (see Chapter 5). In fact, coadministration of other vaccines and of immunostimulants are probably exploiting the same mechanism, i.e., enhancing innate immune mechanisms (see Chapter 2 and 5). An issue that has had little attention is the circadian rhythm of the immune system. In other words, what is the optimal time of the day to receive a vaccine? Some studies have shown a benefit of early morning vaccination, the issue is not settled, and more research is needed here [44,45].

Policy implications

There is a general assumption that responses to vaccinations are seriously weakened in ageing individuals. The response is however surprisingly good with potent new vaccines against zoster and hepatitis B. These vaccines contain novel adjuvants (such as AS04). Also, the mRNA COVID-19 vaccines provide adequate protection in ageing patients, although the responses appear to be waning sooner (as discussed in Chapter 4). This tells us that we are able to develop vaccines that are protective in many older individuals. It also means that we can greatly improve vaccines that are not optimal and highly relevant for old individuals. Existing vaccines that urgently need such improvement are for instance influenza vaccine and pneumococcal vaccine. In older patients with comorbidities, responses to vaccines may vary considerably. In practice this may mean that serological responses should be checked, and vaccination schedules may have to be adapted. In the preceding text, ways to improve vaccination responses in old patients with comorbidities have been indicated.

References

1. Cunningham AL, Lal H, Kovac M, Chlibek R, Hwang SJ, Díez-Domingo J, Godeaux O, Levin MJ, McElhaney JE, Puig-Barberà J, Vanden Abeele C, Vesikari T, Watanabe D, Zahaf T, Ahonen A, Athan E, Barba-Gomez JF, Campora L, de Looze F, Downey HJ, Ghesquiere W, Gorfinkel I, Korhonen T, Leung E, McNeil SA, Oostvogels L, Rombo L, Smetana J, Weckx L, Yeo W, Heineman TC; ZOE-70 Study Group. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. N Engl J Med. 2016 Sep 15;375(11):1019-32
2. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, McGettigan J, Khetan S, Segall N, Solis J, Brosz A, Fierro C, Schwartz H, Neuzil K, Corey L, Gilbert P, Janes H, Follmann D, Marovich M, Mascola J, Polakowski L, Ledgerwood J, Graham BS, Bennett H, Pajon R, Knightly C, Leav B, Deng W, Zhou H, Han S, Ivarsson M, Miller J, Zaks T; COVE Study Group. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021 Feb 4;384(5):403-416. doi: 10.1056/NEJMoa2035389. Epub 2020 Dec 30.
3. Barak Mizrahi, Roni Lotan, Nir Kalkstein, Asaf Peretz, Galit Perez, Amir Ben-Tov, Gabriel Chodick, Sivan Gazit & Tal Patalon. Correlation of SARS-CoV-2-breakthrough infections to time-from-vaccine. Nature Communications volume 12, Article number: 6379 (2021). Published: 04 November 2021.
4. Van Epps P, Tumpey T, Pearce MB, Golding H, Higgins P, Hornick T, Burant C, Wilson BM, Banks R, Gravenstein S, Canaday DH. Preexisting immunity, not frailty phenotype, predicts influenza postvaccination titers among older veterans. Clin Vaccine Immunol. 2017 Mar 6;24(3):e00498-16.
5. Narang V, Lu Y, Tan C, Camous XFN, Nyunt SZ, Carre C, Mok EWH, Wong G, Maurer-Stroh S, Abel B, Burdin N, Poidinger M, Tambyah PA, Bosco N, Visan L, Ng TP, Larbi A. Influenza vaccine-induced

antibody responses are not impaired by frailty in the community-dwelling elderly with natural influenza exposure. Front Immunol. 2018 Oct 24;9:2465.
6. Lee JKH, Lam GKL, Shin T, Samson SI, Greenberg DP, Chit A. Efficacy and effectiveness of high-dose influenza vaccine in older adults by circulating strain and antigenic match: An updated systematic review and meta-analysis. Vaccine. 2021 Mar 15;39 Suppl 1:A24-A35. doi: 10.1016/j.vaccine.2020.09.004. Epub 2021 Jan 7.
7. Cools HJ, Gussekloo J, Remmerswaal JE, Remarque EJ, Kroes AC. Benefits of increasing the dose of influenza vaccine in residents of long-term care facilities: a randomized placebo-controlled trial. J Med Virol. 2009 May;81(5):908-14
8. Vermeiren AP, Hoebe CJ, Dukers-Muijrers NH. High non-responsiveness of males and the elderly to standard hepatitis B vaccination among a large cohort of healthy employees. *J Clin Virol* 2013; **58:** 262–64
9. Remarque EJ, Cools HJ, Boere TJ, van der Klis RJ, Masurel N, Ligthart GJ. Functional disability and antibody response to influenza vaccine in elderly patients in a Dutch nursing home. BMJ. 1996 Apr 20;312(7037):1015. doi: 10.1136/bmj.312.7037.1015.PMID: 8616350
10. Gross PA, Quinnan GV Jr, Weksler ME, Setia U, Douglas RG Jr. Relation of chronic disease and immune response to influenza vaccine in the elderly. Vaccine. 1989 Aug;7(4):303-8
11. Williams RE, Sena AC, Moorman AC, et al. Hepatitis B vaccination of susceptible elderly residents of long-term care facilities during a hepatitis B outbreak. Vaccine. 2012;30:3147–3150
12. Looney RJ, Falsey A, Campbell D, Torres A, Kolassa J, Brower C, et al.. Role of Cytomegalovirus in the T Cell Changes Seen in Elderly Individuals. *Clin Immunol* (1999) 90(2):213–9
13. Almanzar G, Schwaiger S, Jenewein B, Keller M, Herndler-Brandstetter D, Wurzner R, et al. Long-term Cytomegalovirus infection leads to significant changes in the composition of the CD8+ T-Cell repertoire, which may be the basis for an imbalance in the cytokine production profile in elderly persons. *J Virol* (2005) 79 (6):3675–83
14. van den Berg SPH, Warmink K, Borghans JAM, Knol MJ, van Baarle D. Effect of Latent Cytomegalovirus Infection on the Antibody Response to Influenza Vaccination: A Systematic Review and Meta-Analysis. *Med Microbiol Immunol* (2019) 208(3-4):305–21
15. Sheridan PA, Paich HA, Handy J, Karlsson EA, Hudgens MG, Sammon AB, et al. Obesity is associated with impaired immune response to influenza vaccination in humans. *Int J Obes.* (2012) 36:1072–7. doi: 10.1038/ijo.2011.208
16. Callahan ST, Wolff M, Hill HR, Edwards KM, Group NVTEUPVHNVS. Impact of body mass index on immunogenicity of pandemic H1N1 vaccine in children and adults. *J Infect Dis.* (2014) 210:1270–4. doi: 10.1093/infdis/jiu245
17. Neidich SD, Green WD, Rebeles J, Karlsson EA, Schultz-Cherry S, Noah TL, et al. Increased risk of influenza among vaccinated adults who are obese. *Int J Obes.* (2017) 41:1324–30. doi: 10.1038/ijo.2017.131
18. Sheridan PA, Paich HA, Handy J, Karlsson EA, Hudgens MG, Sammon AB, et al. Obesity is associated with impaired immune response to influenza vaccination in humans. *Int J Obes.* (2012) 36:1072–7. doi: 10.1038/ijo.2011.208
19. Cockshott WP, Thompson GT, Howlett LJ, Seeley ET. Intramuscular or intralipomatous injections? N Engl J Med. 1982 Aug 5;307(6):356-8. doi: 10.1056/NEJM198208053070607
20. Rytter MJ, Kolte L, Briend A, Friis H, Christensen VB. The immune system in children with malnutrition--a systematic review. PLoS One. 2014 Aug 25;9(8):e105017. doi: 10.1371/journal.pone.0105017. eCollection 2014.PMID: 25153531
21. Prendergast AJ. 2015 Malnutrition and vaccination in developing countries. Phil. Trans. R. Soc. B 370: 20140141.

22. AlSafar,H.;Grant,W.B.; Hijazi, R.; Uddin, M.; Alkaabi, N.; Tay, G.; Mahboub, B.; Al Anouti, F. COVID-19 Disease Severity and Death in Relation to Vitamin D Status among SARS-CoV-2-Positive UAE Residents. Nutrients 2021, 13, 1714.
23. Michael F Holick. Vitamin D deficiency. N Engl J Med. 2007 Jul 19;357(3):266-81. doi: 10.1056/NEJMra070553.
24. Lee MD, Lin CH, Lei WT, Chang HY, Lee HC, Yeung CY, Chiu NC, Chi H, Liu JM, Hsu RJ, Cheng YJ, Yeh TL, Lin CY. Does Vitamin D Deficiency Affect the Immunogenic Responses to InfluenzaVaccination? A Systematic Review and Meta-Analysis. Nutrients. 2018 Mar 26;10(4):409.
25. Chillon,T.S.;Demircan,K.; Heller, R.A.; Hirschbil-Bremer, I.M.; Diegmann, J.; Bachmann, M.; Moghaddam, A.; Schomburg, L. Relationship between Vitamin D Status and Antibody Response to COVID-19 mRNA Vaccination in Healthy Adults. Biomedicines 2021, 9, 1714.
26. Goncalves-Mendes N, Talvas J, Dualé C, Guttmann A, Corbin V, Marceau G, Sapin V, Brachet P, Evrard B, Laurichesse H and Vasson M-P (2019) Impact of Vitamin D Supplementation on Influenza Vaccine Response and Immune Functions in Deficient Elderly Persons: A Randomized Placebo-Controlled Trial. Front. Immunol. 10:65.
27. Drakesmith H, Pasricha SR, Cabantchik I, Hershko C, Weiss G, Girelli D, Stoffel N, Muckenthaler MU, Nemeth E, Camaschella C, Klenerman P, Zimmermann MB. Vaccine efficacy and iron deficiency: an intertwined pair? Lancet Haematol. 2021 Sep;8(9):e666-e669
28. Muller LM, Gorter KJ, Hak E, et al. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis 2005;41 (3):281–8 [August 1]
29. Huijts SM, van Werkhoven CH, Bolkenbaas M, et al. Post-hoc analysis of a randomized controlled trial: diabetes mellitus modifies the efficacy of the 13-valent pneumococcal conjugate vaccine in elderly. Vaccine. 2017;35:4444–4449
30. Van Der Meeren O, Peterson JT, Dionne M, et al. Prospective clinical trial of hepatitis B vaccination in adults with and without type-2 diabetes mellitus. Hum Vaccin Immunother. 2016;12:2197–2203
31. Goeijenbier M, van Sloten TT, Slobbe L, et al. Benefits of flu vaccination for persons with diabetes mellitus: a review. Vaccine. 2017;35:5095–5101
32. Dos Santos G, Tahrat H, Bekkat-Berkani R. Immunogenicity, safety, and effectiveness of seasonal influenza vaccination in patients with diabetes mellitus: a systematic review. Hum Vaccin Immunother. 2018;14:1853–1866
33. McDonald HI, Thomas SL, Millett ERC, et al. Do influenza and pneumococcal vaccines prevent community-acquired respiratory infections among older people with diabetes and does this vary by chronic kidney disease? A cohort study using electronic health records. BMJ Open Diabetes Res Care. 2017;5:e000332
34. Ocak S, Eskiocak AF. The evaluation of immune responses to hepatitis B vaccination in diabetic and non-diabetic haemodialysis patients and the use of tetanus toxoid. Nephrology (Carlton, Vic). 2008;13:487–491
35. Yousaf F, Gandham S, Galler M, Spinowitz B, Charytan C. Systematic review of the efficacy and safety of intradermal versus intramuscular hepatitis B vaccination in end-stage renal disease population unresponsive to primary vaccination series. Ren Fail. 2015 Aug;37(7):1080-8. Epub 2015 Aug 10.
36. S C Meuer , H Dumann, K H Meyer zum Büschenfelde, H Köhler. Low-dose interleukin-2 induces systemic immune responses against HBsAg in immunodeficient non-responders to hepatitis B vaccination Lancet 1989 Jan 7;1(8628):15-8.
37. Mulley WR, Le ST, Ives KE. Primary seroresponses to double-dose compared with standard-dose hepatitis B vaccination in patients with chronic kidney disease: a systematic review and meta-analysis. Nephrol Dial Transplant. 2017 32(1):136-143
38. Raven S, et al. Serological response to three alternative series of hepatitis B revaccination (Fendrix, Twinrix, and HBVaxPro-40) in healthy non-responders: a multicentre, open-label, randomised, controlled, superiority trial. Lancet Infect Dis, 2020;20:92-101

39. Rincon-Arevalo H, Choi M, Stefanski AL, Halleck F, Weber U, Szelinski F, Jahrsdörfer B, Schrezenmeier H, Ludwig C, Sattler A, Kotsch K, Potekhin A, Chen Y, Burmester GR, Eckardt KU, Guerra GM, Durek P, Heinrich F, Ferreira-Gomes M, Radbruch A, Budde K, Lino AC, Mashreghi MF, Schrezenmeier E, Dörner T. Impaired humoral immunity to SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients and dialysis patients. Sci Immunol. 2021 Jun 15;6(60):eabj1031
40. Garcia Garrido HM, Veurink AM, Leeflang M, Spijker R, Goorhuis A, Grobusch MP. Hepatitis A vaccine immunogenicity in patients using immunosuppressive drugs: A systematic review and meta-analysis. Travel Med Infect Dis. 2019 Sep 12:101479. doi:10.1016/j.tmaid.2019.101479
41. van Aalst M, Langedijk AC, Spijker R, de Bree GJ, Grobusch MP, Goorhuis A. The effect of immunosuppressive agents on immunogenicity of pneumococcal vaccination: a systematic review and meta-analysis. Vaccine 2018;36(39):5832–45
42. Kanis JA, Johansson H, Oden A, et al. A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res 2004; 19:893–99
43. Kunisaki KM, Janoff EN. Influenza in immunosuppressed populations: a review of infection frequency, morbidity, mortality, and vaccine responses. Lancet Infect Dis. 2009 Aug;9(8):493-504. doi: 10.1016/S1473-3099(09)70175-6.PMID: 19628174
44. Zimmermann P, Curtis N. Factors that Influence the immune response to vaccination. Clin Microbiol Rev. 2019 Mar 13;32(2):e00084-18. Print 2019 Mar 20.
45. Kurupati RK, Kossenkoff A, Kannan S, Haut LH, Doyle S, Yin X, Schmader KE, Liu Q, Showe L, Ertl HCJ.Vaccine. 2017 Jun 27;35(30):3700-3708. doi: 10.1016/j.vaccine.2017.05.074. Epub 2017 Jun 2.PMID: 28583307

Chapter 4

Vaccination against COVID-19 in vulnerable groups

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An adequate response to vaccination (or any foreign antigen) requires orchestration of multiple arms of the immune system (see Chapter 2). Typically, and also for the SARS-COV-2 mRNA vaccines, B-cell mediated production of specific antibodies occurs rapidly (humoral immunity) followed by the development of pathogen-directed memory B cells with production of high-specific antibodies and cytotoxic (CD8+) T cells (cellular immunity), that are required for long-term protection. This impressive orchestration requires many more intact immune factors and coordination between them (e.g., antigen-presenting cells, different subtypes of T-helper cells, cytotoxic T cells and B cells, plasma cells, interleukins, interferons, tumor necrosis factors and more).

Vulnerable groups can be divided into: i) those that are immune compromised and ii) those that are immune competent but with comorbidities exposing them to a higher risk for SARS CoV2, complications and fatality.

Immune-compromised patients

Immune-compromised patients may have a higher incidence of vaccine-preventable diseases and a more severe form of the disease. With COVID-19, we do not know whether the risk of infection is higher; studies have not shown a higher risk of contracting COVID-19 among immune compromised patients [1], but the fact that immune-compromised patients may have protected themselves better than the general population was not considered in these analyses. However, they have a higher risk of complications and may have a high risk of death compared to non-immune compromised people, once acquiring COVID-19 [2,3]. Importantly, most immune-suppressed patients have prolonged duration of viral replication during the disease, longer than non-immune compromised people. This has been shown both in COVID-19 and in influenza despite treatment with oseltamivir for the latter [4,5]. Prolonged infection results in mutant strain formation and might result in the development of more virulent mutants, as has been hypothesized regarding the source of the SARS-CoV-2 Alpha variant [6]. Certainly, regardless of the incidence or severity of the infection, any infection may disrupt treatment of the underlying condition, whether the chemotherapy cycle, transplantation or the routine follow-up. Thus, prevention of communicable diseases among immune compromised patients is of a critical priority.

As discussed in Chapter 3, different immune-compromised states affect different components of the immune response to vaccination. The disease itself may interfere when affecting the hematopoietic system, as in leukemias, lymphomas, and multiple myeloma. Different immune suppressants disrupt the normal immune response, from steroids that have broad effects over many of the parts of the immune system to highly specific drugs and monoclonal antibodies that affect a class of immune cells or specific cytokines. In addition to the immune-compromised state, there is the effect of ageing on the vaccine response (discussed in Chapter 3).

Good understanding of the chemotherapy or other immune-suppressants' mechanisms of action, immune-compromised states and the immunological reaction to vaccination may allow prediction of the altered response to vaccination. However, direct proof of vaccine effects requires clinical testing. During the development process of vaccines, up to the Phase 3 trials, immune-compromised patients are excluded. In all randomized controlled trials leading to the COVID-19 vaccine approval, all patients with immune-compromising and immune-modulatory conditions were excluded [7,8], based on the understanding that the response to the vaccine is likely altered among such populations [9]. Effects are also likely heterogenous among different-immune compromised patient groups – solid organ transplant recipients, allogeneic and autologous haematopoetic stem cell transplant recipients, patients with haematological and solid cancers, patients with underlying rheumatological, dermatological, pulmonary or gastrointestinal diseases requiring immune suppression, etc. Variability is possible between each of these conditions and within each condition, complicating possible subgroup analyses of immune-compromised patients. Exclusion by age is probably unjustified, since immunosenescence develops gradually during life and is not fully related to biological age (see Chapter 2). Indeed, old people were included in the recent vaccine-approval trials. The National Institutes of Health (NIH) currently prohibits arbitrary upper age limits on eligibility or exclusion criteria that might preferentially exclude old people from participation in NIH-funded clinical trials [10].

Thus, evidence from the approval randomized controlled trials on vaccine effects in immunocompromised patients is lacking. Yet, such data would be critical and during pandemics obtaining this becomes urgent. We believe it is the pharma companies' obligation to continue vaccine testing in special populations after approval of the vaccine for the general population. It should be a priority to support well-conducted randomized controlled assessing clinical endpoints and observational studies with good immunological testing to understand the ability of the vaccine to prevent disease, reduce its severity and curtail the duration of SARS-COV-2 shedding. While researchers are urgently attempting to address this gap for COVID-19 vaccines [11,12], it should be the regulators' requirement and companies' responsibility to fund larger high-quality trials. These trials need to define the optimal dose, schedule and timing of vaccination in specific risk groups (e.g., need for 3rd vaccine dose for COVID-19, two doses of yearly influenza vaccine, the type and number of doses of the pneumococcal vaccine, optimal timing of vaccination after transplantation or after chemotherapy) and the effect of the tailored vaccination schemes among the different immune-compromised populations. A number of these issues (and additional ones) have been discussed in Chapter 3.

During pandemics, decision makers will sometimes have to take decisions without evidence to support the vaccination strategy of vulnerable groups. The 4th European Conference of Infections in Leukemia (ECIL-4) advises a second seasonal inactivated influenza vaccine for allogeneic or autologous hematopoietic stem cell transplant recipients. As previously discussed, a third COVID-19 vaccine dose is being administered in many countries to patients with a range of immune compromising conditions and in old patients [13,14]. These decisions are taken on the basis of indirect evidence and local considerations (e.g., safety and benefit of the vaccine in the general population, understanding of the vaccine mode of action, the clinical-epidemiological effectiveness of the vaccine, costs and availability). Recognizing the limited ability of highly immune-suppressed patients to amount an immune response, decision makers might also need to recommend the use of passive protection modalities; primarily reducing exposure but also antiviral prophylaxis (as for

influenza) or use of antibody preparations (convalescent plasma or hyper-immune preparations) for COVID-19. These are difficult decisions better taken globally and adopted locally to improve equity.

Immune-competent people vulnerable for COVID-19

Immune-competent individuals may have co-morbidities that enhance the severity of COVID-19 and the risk of death from the disease. Respiratory failure, thrombosis and other complications during COVID-19 can be especially prevalent in patients with diseases that by themselves induce those complications. Among certain patients with malignancies, such as myeloproliferative neoplasms, severity of disease and mortality are increased by thrombotic complications [15,16]. The disease may be prolonged among patients at risk, with a higher prevalence of chronic pulmonary sequela. Many patient groups have identified at risk for severe COVID-19 and death, other than immune-compromised cancer patients, most prominently the old population, but also obese people, people with chronic lung disease, diabetes, chronic kidney disease, various conditions associated with atherosclerosis and others [17].

These patients were included in the RCTs examining vaccine effects and while subgroup analyses by all risk factors are not possible, the effects demonstrated in the RCTs should be considered as relevant for these vulnerable people. Patients identified at risk [17] and those with predisposition to thrombosis should be particularly encouraged to undergo vaccination [18]. Questions currently exist regarding the utility of measuring antibody levels after vaccination, providing a vaccine boost dose and further repeat doses, for all people but especially for vulnerable people.

Global considerations

As of August 2021, 10 countries have administered more than 75% of the world's COVID-19 vaccines, while low-income countries have received just over 1% [19]. This gross inequity in vaccine distribution globally creates populations of vulnerable patients in those countries that have not been able to obtain vaccines. WHO has recently issued a statement against a booster dose at this time, to avoid exacerbation of inequities and promote primary vaccination for vulnerable people globally [20].

In summary, when vaccines enter clinical use after regulatory approval, there is an unavoidable gap in knowledge regarding vaccination in vulnerable patient groups, notably immune-compromised patients. In parallel with the entry of the vaccine into regular use, data on effects among immune-compromised patients must be accrued. This should be required by regulatory agencies and the effort should be supported by the companies producing the vaccines as a standard step of the vaccine approval process. Until evidence accumulates or for small risk groups where no evidence will be available, policy makers must make decisions based on immunological understanding and indirect evidence.

The old people with comorbidities that predispose them to severe COVID-19, if infected with SARS-CoV-2 and people at risk for specific complications, such as thrombosis, should be prioritized and targeted in vaccine campaigns. Attention is needed to address global equity in vaccine availability.

References

1. Tassone D, Thompson A, Connell W, Lee T, Ungaro R, An P, et al. Immunosuppression as a risk factor for COVID-19: a meta-analysis. Intern Med J. 2021;51(2):199-205.

2. Assaad S, Zrounba P, Cropet C, Blay JY. Mortality of patients with solid and haematological cancers presenting with symptoms of COVID-19 with vs without detectable SARS-COV-2: a French nationwide prospective cohort study. Br J Cancer. 2021:1-14.
3. He W, Chen L, Chen L, Yuan G, Fang Y, Chen W, et al. COVID-19 in persons with haematological cancers. Leukemia. 2020;34(6):1637-45.
4. Li T-Z, Cao Z-H, Chen Y, Cai M-T, Zhang L-Y, Xu H, et al. Duration of SARS-CoV-2 RNA shedding and factors associated with prolonged viral shedding in patients with COVID-19. Journal of Medical Virology. 2021;93(1):506-12.
5. Giannella M, Alonso M, Garcia de Viedma D, Lopez Roa P, Catalán P, Padilla B, et al. Prolonged viral shedding in pandemic influenza A(H1N1): clinical significance and viral load analysis in hospitalized patients. Clinical Microbiology and Infection. 2011;17(8):1160-5.
6. Peacock S. Here's what we know about the new variant of coronavirus. The Guardian. 2020.
7. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384(5):403-16.
8. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397(10269):99-111.
9. Simon Galmiche, Liem Binh Luong Nguyen, Eric Tartour, Xavier de Lamballerie, Linda Wittkop, Paul Loubet, Odile Launay. Immunological and clinical efficacy of COVID-19 vaccines in immunocompromised populations: a systematic review. Clinical Microbiology and Infection. 17 November 2021
10. Steinman MA, Boyd CM, Schmader KE. Expanding Evidence for Clinical Care of Older Adults: Beyond Clinical Trial Traditions and Finding New Approaches. JAMA. 2021.
11. Goshen-Lago T, Waldhorn I, Holland R, Szwarcwort-Cohen M, Reiner-Benaim A, Shachor-Meyouhas Y, et al. Serologic Status and Toxic Effects of the SARS-CoV-2 BNT162b2 Vaccine in Patients Undergoing Treatment for Cancer. JAMA Oncology. 2021.
12. Monin L, Laing AG, Muñoz-Ruiz M, McKenzie DR, Del Molino Del Barrio I, Alaguthurai T, et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. Lancet Oncol. 2021;22(6):765-78.
13. The United States Food and Drug Administration (FDA). Coronavirus (COVID-19) Update: FDA Authorizes Additional Vaccine Dose for Certain Immunocompromised Individuals 2021 [Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-vaccine-dose-certain-immunocompromised.
14. Israeli Ministry of Health. Coronavirus 2021 [Available from: https://www.gov.il/en/departments/topics/corona-main-sub.
15. Passamonti F, Cattaneo C, Arcaini L, Bruna R, Cavo M, Merli F, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. The Lancet Haematology. 2020;7(10):e737-e45.
16. Breccia M, Piciocchi A, De Stefano V, Finazzi G, Iurlo A, Fazi P, et al. COVID-19 in Philadelphia-negative myeloproliferative disorders: a GIMEMA survey. Leukemia. 2020;34(10):2813-4.
17. Centers for Disease Control and Prevention. Science Brief: Evidence used to update the list of underlying medical conditions that increase a person's risk of severe illness from COVID-19 2021 [Available from: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/underlying-evidence-table.html.
18. Conseil d'Orientation de la Stratégie Vaccinale: Recommandations pour la protection des personnes sévèrement immunodéprimées contre le Covid-19 (Vaccination et prophylaxie primaire) – 19 Novembre 2021.
19. Tedros AG. Why There Should Be a Moratorium on COVID-19 Booster Shots Until Low-Income Countries Get Vaccinated. Time. 2021 AUGUST 12, 2021.
20. World Health Organization (WHO). Interim statement on COVID-19 vaccine booster doses 2021 [Available from: https://www.who.int/news/item/10-08-2021-interim-statement-on-covid-19-vaccine-booster-doses.

Chapter 5

Vaccine adjuvants

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Nearly a century ago it was noted that vaccine responses in guinea pigs were enhanced when alum was included in the vaccine. This was a serendipitous finding, since the alum was added to precipitate the diphtheria toxoid [1]. Later on, other substances have been observed to display similar properties, including mixtures of paraffin oil in water (incomplete Freund adjuvant) without or with the addition of microbial structures (complete Freund adjuvant) [2]. Such substances that improve the efficacy of antigens used in vaccines to induce a long-term immune memory response were termed adjuvants, i.e., substances that are able to enhance the immune response against the vaccine.

Currently, the following adjuvants are licensed for use in humans: Alum, MF59, AS03, AS04, AF03, virosomes and heat labile enterotoxin. Quite a number of new adjuvants are in development, including Toll-like receptor ligands such as lipopolysaccharide or nucleic acid mimetics. Not all vaccines need an adjuvant to elicit a protective immune response. Live vaccines in particular do not need the addition of an adjuvant. In fact, these vaccines tend to have adjuvant effects themselves. This has been demonstrated in studies where vaccines such as influenza vaccine and yellow fever vaccine were combined with Bacillus Calmette-Guérin (BCG) [3]. Adjuvants are especially important for populations with a poor immune response. In ageing individuals, it has been demonstrated that some of the newer adjuvants like AS04 (present in the hepatitis B vaccine) and AS01 (in the zoster vaccine) and MF59 (in the Trivalent inactivated influenza vaccine) are able to enhance the vaccine response. Systematic studies exploring the optimal adjuvants for vaccines that are relevant for older people are very much needed. Adjuvants may also speed up the immune response to a vaccine, a property which may be of help in an epidemic.

How do adjuvants work?

There is a comprehensive literature on the immunological effects of the various adjuvants. It is relevant to note, however, that despite a lot of experimental work, we still do not know the exact mechanisms by which the various adjuvants enhance the protective vaccine responses. A detailed review on their immunological mechanisms is beyond the scope of this chapter. In general, most adjuvants enhance both the non-specific immune responses and the specific immune responses. There is evidence for the following mechanisms [4]:

- Sustained release of antigen at the site of injection (depot effect),
- Enhanced production and release of cytokines and chemokines, e.g., by ligation of Toll-like receptors and/or activation of inflammasomes
- Recruitment of cells of the immune system at the vaccination site
- Increased antigen uptake and presentation to antigen presenting cells

- Increased expression of major histocompatibility complex (MHC) class II and co-stimulatory molecules leading to activation and maturation of antigen presenting cells
- Enhanced migration to the draining lymph nodes

The relative contribution of these mechanisms is still a matter of debate. Many of the mechanisms listed above represent proinflammatory, non-specific responses. In older patients, it is reasonably well established that inflammatory responses are enhanced. Thus, one might expect that adjuvants work well in older patients, but as has already been said, more research is needed here.

Enhancement of innate immunity and heterologous protection by vaccines

One aspect of vaccines that has only recently started to be studied is that of the heterologous protective effects that some vaccines (especially whole microorganism or live attenuated vaccines) may induce. It has already been shown in early epidemiological studies since BCG vaccine (the live vaccine against tuberculosis) was introduced in the population one century ago, that it has an impressive protective effect against mortality and infections other than tuberculosis in children [5]. The early observational studies were later corroborated in a seminal clinical study by Aaby and Benn performed in African children, in which BCG clearly protected against a variety of infections and met with a survival benefit [6]. While the immunological mechanisms underlying these observations was unclear for a long period of time, recent years have witnessed the discovery of important molecular mechanisms represented by long-lasting epigenetic and functional reprogramming of immune cells, especially monocytes and macrophages. This phenomenon has been termed 'trained immunity' (or trained innate immunity) [7] and has been proposed to largely explain the heterologous protective effects of vaccination. While heterologous protective effects by live attenuated vaccines (such as BCG, measles-containing vaccines or oral polio vaccine) are now largely accepted in children [8], the breadth of these effects in older individuals is less well known. A number of recent studies have reported a decrease in respiratory tract infections in adults or ageing individuals after revaccination with BCG [9,10], but larger dedicated trials with several of the attenuated vaccines are needed in order to assess the overall potential of heterologous vaccination in older populations.

References

1. Glenny AT, Pope CG, Waddington H, Wallace U. Understanding Disease. The Journal of Pathology. 1 January 1926; 29:31–40. doi:10.1002/ path.1700290106
2. Billiau A, Mathys P. Modes of action of Freund's adjuvants in experimental models of autoimmune diseases. Journal of Leukocyte Biology. December 2001, 849, Vol. 70
3. Arts RJW, Moorlag SJCFM, Novakovic B, Li Y, Wang SY, Oosting M, Kumar V, Xavier RJ, et al. BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity. Cell Host Microbe. 2018 Jan 10;23(1):89-100.e5. doi: 10.1016/j.chom.2017.12.010. PMID: 29324233.
4. Shi S, Zhu H, Xia X, Liang Z, Ma X, Sun B. Vaccine adjuvants: Understanding the structure and mechanism of adjuvanticity. Vaccine. 27 May 2019, Vol 37:24, 3167-317, https://doi.org/10.1016/j.vaccine.2019.04.055
5. Institut Pasteur. Vaccination préventive de la tuberculose de l'homme et des animaux, par le BCG : rapports et documents, provenant des divers pays. 1932, pp. 274–281
6. Benn CS, Netea MG, Selin LK, Aaby P. A small jab - a big effect: nonspecific immunomodulation by vaccines. Trends Immunol. 2013 Sep;34(9):431-9. doi: 10.1016/j.it.2013.04.004.

7. Quintin J, Saeed S, Martens JHA, Giamarellos-Bourboulis EJ, Ifrim DC, Logie C, Jacobs L, Jansen T,et al. Candida albicans infection affords protection against reinfection via functional reprogramming of monocytes. Cell Host Microbe. Aug 2012,16;12(2):223-32. doi: 10.1016/j.chom.2012.06.006.
8. Higgins J P T, Soares-Weiser K, Lopez-Lopez JA, Kakourou A, Chaplin K, Christensen H et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. BMJ. 2016; 355:5170, doi:10.1136/bmj.i5170
9. Nemes E, Geldenhuys H, Rozot V, Rutkowski KT, Ratangee F, Bilek N, Mabwe S, Makhethe L, Erasmus M, et al. Prevention of M. tuberculosis Infection with H4:IC31 Vaccine or BCG Revaccination. N Engl J Med. 2018 Jul 12;379(2):138-149. doi: 10.1056/NEJMoa1714021.
10. Giamarellos-Bourboulis EJ, Tsilika M, Moorlag S, Antonakos N, Kotsaki A, Domínguez-Andrés J, Kyriazopoulou E, et al. Activate: Randomized Clinical Trial of BCG Vaccination against Infection in the Elderly. Cell. 2020 Oct 15;183(2):315-323.e9. doi: 10.1016/j.cell.2020.08.051

Chapter 6

Potential of mRNA vaccines in the old population

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Until recently, vaccines used technologies based on attenuated or inactivated virus or bacteria, or on sub-unit extracts or recombinant proteins. These vaccines require a very complex and long process of production and are poorly adapted to achieve rapid protection against viruses that continuously evolve such as influenza or new emerging virus variants. On the contrary, nucleic acid-based vaccines, such as mRNA vaccines, together with viral or plasmid DNA vectors, have the potential for solving these needs because they hold a quick malleability of the targeted antigen design (the nucleic acid sequence) and because they are rapidly scalable in high-volume manufacturing. However, before the recent pandemic, these technologies were not evaluated in older adults, a population very much at risk of severe disease.
The COVID-19 pandemic has unlocked in early 2020 the extraordinary power of nucleic acid vaccines and, by an amazing rush of all developmental research steps, new vaccines (mRNA and vectored) became licensed in less than a year to be used in millions of humans, among which old adults were the priority.

mRNA-based vaccines, a key research milestone for vaccinology

The idea of using an mRNA fragment to induce specific protein translation in vivo, with the goal of inducing a physiological response, dates back to 1988, when an mRNA coupled to a lipid-based vector, an oil droplet, could be adsorbed, and use cellular machinery to be translated into the targeted protein [4,5]. Since then, a completely new therapeutic strategy based on RNA transfection became possible and this method started to be used to specifically induce immune responses, in animal models [6,7]. Definitely, after being transfected, these mRNAs expressed high levels of proteins and conferred highly effective and long-lasting immunity in both newborn and elderly animal models [6,7], opening new hope for immune protection against pathogens that causes epidemic outbreaks, as for instance against viruses that evade adaptive immune responses (Zika, Ebola, influenza, and SARS).
Before the Covid 19 outbreak, mRNA vaccines for seasonal influenza A, which kills, thousands of old people every year, have been investigated in both preclinical and early phase studies [8,9]. Furthermore, safety and robust immune responses to mRNA vaccines against H10N8 and H7N9 influenza virus strains, potentially pandemic strains, greatly supported the potential of mRNA vaccine platform for being easy, malleable, and able to confer a good immune response against all influenza strains [10]. However, despite the preclinical

success, the number of human trials that have explored mRNA vaccines remains quite limited, especially in the older population. The mRNA vaccines targeting Rabies, Zika, Ebola, Influenza as well as multivalent antigens mixtures, and vaccines targeting bacteria or parasites are all into clinical evaluation [11], but none of them has been approved or is available yet.

mRNA SARS-Cov2 vaccines

In 2020, two mRNA-based SARS-Cov-2 vaccines (BNT162b2, and mRNA-1273, respectively from Pfizer/BioNTech and Moderna), were approved. The two vaccines showed a very high efficacy in phase 3 clinical trials to prevent SARS-Cov-2 infection after 2 doses of vaccines (95% and 94,1%, for BNT162b2, and mRNA-1273, respectively in the global study population, and 94,7% and 86,4% in adults more than 65 years old) [10,11], an acceptable tolerability, good immunogenicity in terms of antibody production early after vaccination - however lower in old than young adults while safety is equivalent [12,14]. For both mRNA-1273 and BNT162b2 vaccines, a two-dose regimen has proven its efficacy and safety [12,13] and the need for the second dose has been quickly ascertained [15,16]. The vaccination campaign started at the end of 2020 or in the beginning of 2021 worldwide, starting with at risk populations, and concerning the more aged vulnerable people, living in nursing home. This led to greatly reduced mortality in this population, which before vaccination were dying at amazing speed [17,18]. However, vaccine efficacy declines over time, especially in old population. For instance, in a real-life study using BNT162b2 from 7 days to less than 2 months after the second dose, vaccine efficacy was 96.2%; from 2 months to less than 4 months after the second dose, vaccine efficacy was 90.1% and from 4 months after the second dose to the data cut-off date, vaccine efficacy was 83.7% [19]. Furthermore, 17 days after the second vaccination with Pfizer vaccine, 31.3 % of the older population had no detectable neutralizing antibodies, on the contrary in the younger group only 2.2% had no detectable neutralizing antibodies, suggesting that revaccination or/and an increased vaccine dose in older people is needed to guarantee a solid long-lasting immunity [20]. In another observational study in English healthcare workers, a deeper exploration of the immune response in young versus older people revealed possible explanations for their poorer neutralizing responses [21]; notably, beside lower concentrations of antibodies the lower-affinity antibodies were correlated with a different B cell selection in elders compared to young, also cytokine secretion by T cells (both interleukin-2 and interferon-γ) were lower in older participants, suggesting reduced $CD4^+$ T cell help. These data parallel those obtained in animal model data using aged mice versus young, where vaccine responses were reported to be lower than in younger mice. This was overcome by booster dosing further confirming the low protection in old adults and the booster requirement but pointing also to the importance of a deep immune-monitoring follow up of all vaccine induced immune responses [21].

Long term mRNA vaccine immunogenicity and efficacy in the old population

The follow up of antibody persistence in trials using either BNT162b2 and mRNA-1273 revealed, although a quite durable persistence of antibodies, a significant reduction in neutralisation assays in the older population [21-23]. In particular, at 6 months after the second dose, binding antibodies, measured by means of classical enzyme-linked immunosorbent assay against SARS-CoV-2 spike receptor–binding domain in sera of participants vaccinated with mRNA-1273, were of 92,451 (95% confidence interval [CI], 57,148 to 149,562) in participants 18 to 55 years of age, 62,424 (95% CI, 36,765 to 105,990) in those 56 to 70 years of age, and 49,373 (95% CI, 25,171 to 96,849) in those 71 years of age or older [22]. A substantial reduction in the IgG level each month, which culminated in a decrease by a factor of 18.3 after 6 months, was also observed in the sera of participants vaccinated with BNT162b2 [23]. Neutralizing antibodies were also shown to decay, even though at different kinetics compared to total IgG decay, and more in older persons as well as in other high-risk populations (immunosuppression, more than one comorbidity). Decreases in IgG and neutralizing antibody concentrations were of 38% and 42%, respectively, among persons of 65 years old or older as compared with participants of 18 - 45 years of age. Together with reduced antibody levels and activity a

reduced binding potential of the antibodies against variants of concern was also revealed [24,25], suggesting that SARS-CoV-2 variants, Delta *in primis*, display a reduced sensitivity to vaccine induced neutralizing antibodies [26-28]. Indeed, it was suggested that higher levels of antibodies better correlate with enhanced binding of neutralizing antibodies to variant antigens, thus a third dose boost is essential to ensure protection in older people, and particularly to assure protection against new circulating variants. Preliminary reports revealed that rates of confirmed infections and severe illness were substantially lower among groups who received a booster dose of the BNT162b2 vaccine, and this, in the context of the high prevalence of delta variants, providing so indirect evidence for the effectiveness of the booster dose against the currently dominant delta variant in young, as well as in 60+ years old people [29-31]. Following FDA and EMA authorisations together with WHO and local governmental recommendations, and in line with ongoing interim results, the booster dose is being recommended worldwide and administered in old and in all at risk populations [29].

Perspectives

The COVID 19 outbreak greatly motivated the revolutionary development of mRNA vaccines with amazing speed over both scientific and clinical research. mRNA vaccine technology possesses a rapid, flexible, and easy scalable manufacturing process and mRNA vaccines against SARS-CoV2 proved their efficacy in young, but also in old and very old populations. The impressive and unexpected efficacy of this new generation of vaccines in the more aged populations opens up the hope that this new revolutionary technology may encourage a more global advance in vaccine research and thus help achieve an overall better protection of older adults through vaccination [32]. Still, the persistence of protection in frail populations needs to be further explored and probably improvement of the induced immune responses by new formulations, or new vaccine combinations will be needed, especially to ameliorate the repertoire diversity as well T and B cells responses. Several research projects are ongoing to track protection over time, as for example to correct all along the vaccination campaign progression, the overall vaccination strategy, and the booster timing for the older population. Another interesting option for successful vaccination may arise from heterologous vaccinations combining different platform vaccines, as for instance for boosting. On this matter, prime boost pioneering studies showed that a sequential immunization with adenovirus vectored vaccine followed by inactivated/recombinant subunit/mRNA vaccine administration increased levels of neutralizing antibodies [33]. Moreover, a heterologous prime boost regimen with an adenovirus vector vaccine also improved T cell responses. Ongoing and upcoming trials with heterologous combination will explore different vaccine combinations for further vaccine strategy improvement. To address some of these concerns, we also designed the CoviCompare project, which consists of a comprehensive longitudinal analysis of the various components of innate and adaptive immune responses induced by different vaccine platforms in older compared to younger individuals. Today current vaccines for seasonal influenza A are poorly efficacious, with influenza being still among the principal killer of the old population. Nucleic acid-based vaccines such as mRNA, but also viral vectors or plasmid DNA based vaccines explored today in SARS-Cov-2 vaccine research will surely help speed forward Influenza vaccine research and save even more older lives.

References

1. Ciabattini, A*., et al.* Vaccination in the elderly: The challenge of immune changes with aging. *Semin Immunol* 40, 83-94 (2018).
2. Weyand, C.M. & Goronzy, J.J. Immune mechanisms in medium and large-vessel vasculitis. *Nat Rev Rheumatol* 9, 731-740 (2013).
3. Franceschi, C*., et al.* Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci* 908, 244-254 (2000).

4. Malone, R.W., Felgner, P.L. & Verma, I.M. Cationic liposome-mediated RNA transfection. *Proc Natl Acad Sci U S A* 86, 6077-6081 (1989).
5. Martinon F, Krishnan S, Lenzen G, Magné R, Gomard E, Guillet JG, Lévy JP, Meulien P. Induction of virus-specific cytotoxic T lymphocytes in vivo by liposome-entrapped mRNA. Eur J Immunol. 1993 Jul;23(7):1719-22. doi: 10.1002/eji.1830230749. PMID: 8325342.
6. Kariko, K., Buckstein, M., Ni, H. & Weissman, D. Suppression of RNA recognition by Toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA. *Immunity* 23, 165-175 (2005).
7. Wolff, J.A.*, et al.* Direct gene transfer into mouse muscle in vivo. *Science* 247, 1465-1468 (1990).
8. Pardi, N. & Weissman, D. Nucleoside Modified mRNA Vaccines for Infectious Diseases. *Methods Mol Biol* 1499, 109-121 (2017).
9. Scorza, F.B. & Pardi, N. New Kids on the Block: RNA-Based Influenza Virus Vaccines. *Vaccines (Basel)* 6(2018).
10. Feldman, R.A.*, et al.* mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. *Vaccine* 37, 3326-3334 (2019).
11. Maruggi, G., Zhang, C., Li, J., Ulmer, J.B. & Yu, D. mRNA as a Transformative Technology for Vaccine Development to Control Infectious Diseases. *Mol Ther* 27, 757-772 (2019).
12. Baden, L.R.*, et al.* Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* 384, 403-416 (2021).
13. Polack, F.P.*, et al.* Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 383, 2603-2615 (2020).
14. Anderson, M.*, et al.* SARS-CoV-2 Antibody Responses in Infection-Naive or Previously Infected Individuals After 1 and 2 Doses of the BNT162b2 Vaccine. *JAMA Netw Open* 4, e2119741 (2021).
15. Terpos, E.*, et al.* Age-dependent and gender-dependent antibody responses against SARS-CoV-2 in health workers and octogenarians after vaccination with the BNT162b2 mRNA vaccine. *Am J Hematol* 96, E257-E259 (2021).
16. Widge, A.T.*, et al.* Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. *N Engl J Med* 384, 80-82 (2021).
17. Vasileiou, E.*, et al.* Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. *Lancet* 397, 1646-1657 (2021).
18. Victora, P.C.*, et al.* Estimating the early impact of vaccination against COVID-19 on deaths among elderly people in Brazil: Analyses of routinely-collected data on vaccine coverage and mortality. *EClinicalMedicine* 38, 101036 (2021).
19. Thomas, S.J.*, et al.* Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. *N Engl J Med* (2021).
20. Muller, L.*, et al.* Age-dependent immune response to the Biontech/Pfizer BNT162b2 COVID-19 vaccination. *Clin Infect Dis* (2021).
21. Collier, D.A.*, et al.* Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. *Nature* 596, 417-422 (2021).
22. Doria-Rose, N.*, et al.* Antibody Persistence through 6 Months after the Second Dose of mRNA-1273 Vaccine for Covid-19. *N Engl J Med* 384, 2259-2261 (2021).
23. Levin, E.G.*, et al.* Waning Immune Humoral Response to BNT162b2 Covid-19 Vaccine over 6 Months. *N Engl J Med* (2021).
24. Edara, V.V.*, et al.* Infection and vaccine-induced neutralizing antibody responses to the SARS-CoV-2 B.1.617.1 variant. *bioRxiv* (2021).
25. Planas, D.*, et al.* Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. *Nature* 596, 276-280 (2021).
26. Goldberg, Y.*, et al.* Waning immunity of the BNT162b2 vaccine: A nationwide study from Israel. *medRxiv*, 2021.2008.2024.21262423 (2021).
27. Puranik, A.*, et al.* Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. *medRxiv*, 2021.2008.2006.21261707 (2021).

28. Tang, P., *et al.* BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the Delta (B.1.617.2) variant in Qatar. *medRxiv*, 2021.2008.2011.21261885 (2021).
29. Bar-On, Y.M., *et al.* Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. *N Engl J Med* 385, 1393-1400 (2021).
30. Levine-Tiefenbrun, M., *et al.* Viral loads of Delta-variant SARS-CoV2 breakthrough infections following vaccination and booster with the BNT162b2 vaccine. *medRxiv*, 2021.2008.2029.21262798 (2021).
31. Barda N, Dagan N, Cohen C, Hernán MA, Lipsitch M, Kohane IS, Reis BY, Balicer RD. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. Lancet. 2021 Dec 4;398(10316):2093-2100. doi: 10.1016/S0140-6736(21)02249-2. Epub 2021 Oct 29. PMID: 34756184; PMCID: PMC8555967.
32. Rauch, S., Jasny, E., Schmidt, K.E. & Petsch, B. New Vaccine Technologies to Combat Outbreak Situations. *Front Immunol* 9, 1963 (2018).
33. He, Q., *et al.* Heterologous prime-boost: breaking the protective immune response bottleneck of COVID-19 vaccine candidates. *Emerg Microbes Infect* 10, 629-637 (2021).

Chapter 7

The challenge of vaccine acceptance in the old population

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Vaccinating a majority of the population is easier than reaching the last pockets of unvaccinated people, the unwilling or weakly motivated. This observation can be made in countries where the vaccination coverage of seniors against COVID-19 is not 100%, and where the vaccination coverage against seasonal influenza does not reach 75% in people over 65 years of age, despite clear recommendations and vaccine availability. Vaccine hesitancy may contribute to suboptimal vaccine coverage in adults over 65 years old. In 2019, the World Health Organization identified vaccine hesitancy as one of the ten major issues for global health [1]. According to WHO Strategic Advisory Group of Experts on Immunization working group, "*vaccine hesitancy refers to delay in acceptance or refusal of vaccines despite availability of vaccine services. Vaccine hesitancy is complex and context specific, varying across time, place and vaccine"* [2]. Vaccine hesitancy was mainly explored in the context of childhood immunization. Rates of vaccine coverage seasonal influenza, pneumococcus and shingles in adults and particularly the older population are all insufficient in the European Union. Seasonal influenza vaccine coverage remains under the target of 75 % in Europe for older age groups, with large discrepancies between countries, and few countries reaching the target [3]. In the context of COVID-19, the older population was one of the first identified target groups with healthcare workers for vaccination. Before the launch of the COVID-19 vaccine campaign, COVID-19 vaccine acceptance was higher in the older age groups. The European Council for Disease Control and Prevention (ECDC) currently tracks cumulative uptake of COVID-19 vaccine in adults aged 60 years and above [4]. This rate reached a glass ceiling with 86.9 % of adults over 60 years having received a full vaccination against COVID-19. Large discrepancies are observed with COVID-19 vaccine coverage in this population ranging from 32.9 % in Bulgaria and close to 100 % in Malta, Spain, Portugal, Ireland, Iceland, Denmark.

Vaccine refusal and vaccine hesitancy

Individuals who refuse a vaccine are not necessarily "anti-vaxxers" [5], they could be only "vaccine-hesitant". Vaccine-hesitant individuals are a heterogeneous group with some individuals refusing all the vaccines, and other individuals refusing some vaccines and agreeing to others, arguing doubts about safety and efficacy. In 2018, the Federation of European Academies of Medicine (FEAM) had distinguished: Vaccine rejecters, Vaccine resistant and Vaccine hesitant [6]. Vaccine rejecters refuse vaccine information and may believe in conspiracy theories. Vaccine resistants may consider vaccine information. Vaccine hesitants had anxiety

about vaccine and safety concerns are the main barriers to vaccine uptake. Different determinants of vaccine hesitancy have been described. In the 3C model of the WHO SAGE working group, *Confidence* refers to trust in a vaccine, in the system of vaccine delivery and in vaccine policy makers, *Complacency* refers to a low perceived risk of vaccine-preventable diseases, *Convenience* refers to vaccine availability, accessibility, and affordability. *Convenience* might be crucial in the context of the COVID-19 vaccine roll-out, inequalities in access to vaccines or to vaccine services may have contributed to insufficient vaccine coverage in the old population in France. In a study (submitted), individuals over 65 years of age and living in rural area were less likely to be vaccinated against COVID-19 than individuals living in urban settings [7]. Two additional psychological antecedents may contribute: *Calculation* refers to individual's engagement in the decision making by searching information and *Collective responsibility* refers to the social benefits of vaccination [8]. The Vaccine Confidence project regularly assesses the state of vaccine confidence in the European Union [9]. In 2018, 82.1% of the respondents considered vaccines in general as safe, with disparities observed between countries, this proportion was the lowest in Bulgaria, Latvia, and France (66.3, 68.2, and 69.9 % respectively). In Denmark, Portugal, and Spain more than 90 % of the respondents considered vaccines as safe. In these three countries, a high level of confidence in vaccine effectiveness was also observed. In contrast, in Latvia, Bulgaria, and Poland, more than 25 % of the respondents had doubts about vaccine effectiveness. The Vaccine Confidence project focused on seasonal influenza vaccine, recommended in most of European countries in adults over 65 years of age. Only 61.7 % of the respondents considered that seasonal influenza vaccine is important in Romania; in the United Kingdom and in Portugal, this proportion is close to 80-90 %. Only 67.8 % of the respondents considered seasonal influenza vaccine as safe; once again, confidence in seasonal influenza vaccine safety was greater in the United Kingdom, Portugal, and Spain. The highest vaccine coverage against seasonal influenza was reached in the United Kingdom. Almost all the older populations had received COVID-19 vaccine in Spain, Portugal, and Denmark. At the opposite extreme, in countries where vaccine confidence is lower, such as in Latvia, Poland and France, a significant proportion of the old population (over 80 years of age) did not receive any COVID-19 vaccine dose, ranging from 15 % in France to 40 % in Poland. These observations are in favor of the fact that confidence plays a crucial role in the decision-making process for immunization in the old population.

Barriers and motivators to vaccination

In the older population, intentions to vaccinate were explored in different contexts: seasonal influenza, prevention of pneumococcal disease, shingles, and COVID-19. It is frequently observed that socio-demographics factors such as female gender, marital status (single), ethnic minority and low socioeconomic and educational levels are associated with non-vaccination or vaccine refusal. Beyond these socio-demographics factors, Yaqub *et al.* reviewed reasons underlying vaccine attitudes in the general population [10]. Some barriers and motivators are particularly relevant in the older population (**Table 1**). Self-protection, perceived severity of the disease and perceived high susceptibility to the disease contribute to attitudes toward vaccination. In the context of the COVID-19 pandemic and its high burden in older people, these motivators may in part explain the high level of COVID-19 vaccine acceptance in older individuals [11,12]. Perceived susceptibility and severity of the vaccine preventable diseases are based on patients' awareness and previous knowledge of the disease but are also subjective. In contrast, perceived low severity of the illness, low susceptibility to the infection and perceived ineffectiveness of the vaccine are often reported as barriers to vaccination [10]. The perceived ineffectiveness of the vaccine is particularly of interest in the context of seasonal influenza vaccination and may become a concern for COVID-19 vaccination with publication about the risk of infection in vaccinated individuals. Developing an accurate communication strategy will be necessary to encourage older individuals to get booster doses without affecting their confidence, and easy access will do so.

Social norms and advice from friends and family are also significant motivators for vaccine acceptance [10]. In the older population, particularly individuals living in long-term care facilities, collecting informed consent and the role of the family in the decision making are ethical issues [13,14]. Concerns about vaccine safety are the most frequently reported barrier to vaccination. In a recent French Study (submitted) in individuals over 65 years of age, concerns about COVID-19 vaccine safety and the fact that the vaccine was so quickly developed were the main barriers to vaccine uptake [7]. In addition, use of or beliefs in complementary medicines are associated with vaccine refusal, particularly homeopathy, naturopathy [15]. Lack of knowledge and poor information about the illness and the vaccine are often reported as barriers to vaccination [10]. Distrust in pharmaceutical companies, health authorities and governments are also described as barriers to vaccination [10]. In the context of the COVID-19, the public debate about COVID-19 vaccination is polarized, and partisans from non-governmental parties are less prone to get vaccinated [16,17]. The politicization of the COVID-19 vaccine was also identified in people over 65 years of age (submitted) [7].

Barriers	Motivators
Socio-demographic factors: lower educational levels, female gender, single status, ethnic minorities, low socio-economic conditions	Socio-demographic factors: higher socio-economic levels, higher educational levels
Mistrust in authorities	Knowledge about the vaccine preventable disease, self-protection
Safety concerns Concerns about vaccine effectiveness	Social norms, collective responsibility
Complacency: low perceived risk of susceptibility to the vaccine preventable disease	Healthcare workers recommendation
Vaccine costs	Accessibility (appointments,

Table 1: Examples of barriers and motivators for vaccination in the old population

Role of Healthcare workers

Recommendation by a healthcare provider (HCP) is one of the main drivers for vaccine decision making [10]. However, vaccine hesitancy may also affect HCPs as general practitioners [18]. HCPs may also experience difficulties in communicating about vaccines with their patients and these difficulties were recently reviewed [19]. HCP face different type of attitudes in patients ranging from vaccine rejecters to great demanders [19]. Beyond vaccine hesitancy, the concept of vaccine apathy has emerged [20] defined as a disinterest characterized by weak attitudes and little time spent considering vaccination. Older patients are also exposed to fake news and HCP should deal with misinformation, concerns about vaccine safety in older patients. Personal views of HCPs about the vaccine-preventable diseases may also play a role in their ability to recommend a vaccine to older patients. A HCP who personally experienced a case of severe influenza is probably more likely to recommend Flu vaccine. Vaccine counseling in older patients is a time-consuming activity, and there are HCPs who do not prioritize this activity due to lack of time. HCPs also report limited knowledge about vaccination for older adults [19]. HCPs also declared that guidelines are frequently changing and discrepancies between countries and regions are confusing [19].

A framework to obtain a high and equitable vaccine uptake

In 2017, face to measles epidemics and low seasonal influenza vaccine coverage, the European Commission launched an initiative entitled "Strengthened cooperation against vaccine preventable diseases". In this context, the European Academies Science Advisory Council (EASAC), and the Federation of European Academies of Medicine (FEAM) made ten recommendations [6]. The first recommendation is to investigate the reasons for low and decreasing vaccine uptake at the level of EU Member States in order to develop tailor-made interventions, involving social scientists. The World Health Organization (WHO) developed a Tailoring Immunization Programs (TIPS) approach for the European Region in 2019. The approach may help to identify target groups (groups with low vaccine coverage), to identify barriers and drivers to vaccination, and to design evidence-based interventions for high and equitable vaccination uptake. This framework identified principles, a theoretical model, and the different phases of a program to insure a high and equitable vaccine uptake in Europe [21]. The six principles are:

- Equity: ensuring equal access and utilization of vaccination services.
- Participatory: stakeholders should be involved and share their experience
- Comprehensive approach: A TIP should be based on theoretical models considering all barriers and motivators
- Evidence: A TIP should be evidence-based
- Health goals
- People-centered.

In the TIP, a behavior change model was adapted to vaccination, the COM-B Model regroups different factors affecting vaccine behavior: the Capability, the Opportunity and the Motivation (**Table 2**). Interventions to increase vaccine uptake should address the different factors identified. In 2017, the European Centre for Disease Prevention and Control published a catalogue of interventions addressing vaccine hesitancy [22]. Most of the interventions were related to childhood immunization. Interventions addressing vaccine hesitancy in the older population should be developed and evaluated. In addition, in the context of COVID-19, WHO had also developed a guide entitled "Data for action: achieving high uptake of COVID-19 vaccines" [23], that may help to harmonize research about COVID-19 acceptance worldwide.

Capability	Motivation	Opportunity
Physical capability	Individual perceived risk	Social norms
Knowledge about the disease	Confidence	Accessibility
Knowledge about the vaccine	Concerns	Systems
	Healthcare professional's recommendation	Costs

Table 2: COM-B models factors in the context of the elderly

The prevention of infectious diseases by vaccination contributes to healthy aging [21]. This factual statement is not always evident to the older population and HCPs. Researchers have paid great attention to childhood immunization and vaccine hesitancy in parents. Interest in the issue of vaccine hesitancy in seniors is growing in the context of COVID-19, and research carried out in this context might have an impact for other vaccines: seasonal influenza, shingles, and pneumococcus. It is time to place vaccination in the care of the oldest patients. It is necessary to restore confidence about the safety and effectiveness of vaccines in this population, their caregivers and in the population of HCPs (GPs, physicians, nurses, and pharmacists), involved in the care of older individuals. Measuring vaccine hesitancy and evaluating attitudes toward

vaccines in the older population are necessary to develop different interventions targeting both older individuals and HCPs.

References

1. Ten health issues WHO will tackle this year [Internet]. [cited 2020 Apr 3]. Available from: https://www.who.int/news-room/feature-stories/ten-threats-to-global-health-in-2019
2. MacDonald NE, SAGE Working Group on Vaccine Hesitancy. Vaccine hesitancy: Definition, scope and determinants. Vaccine. 2015 Aug 14;33(34):4161–4.
3. Seasonal influenza vaccination and antiviral use in EU/EEA Member States [Internet]. European Centre for Disease Prevention and Control. 2018 [cited 2021 Sep 20]. Available from: https://www.ecdc.europa.eu/en/publications-data/seasonal-influenza-vaccination-antiviral-use-eu-eea-member-states
4. COVID-19 Vaccine Tracker | European Centre for Disease Prevention and Control [Internet]. [cited 2021 Sep 20]. Available from: https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#target-group-tab
5. Larson HJ, Broniatowski DA. Volatility of vaccine confidence. Science. 2021 Mar 26;371(6536):1289–1289.
6. Vaccination in Europe – A joint FEAM/EASAC Commentary on the European Commission Roadmap on Strengthened cooperation against vaccine preventable diseases | FEAM [Internet]. [cited 2021 Nov 30]. Available from: https://www.feam.eu/vaccination-in-europe/
7. Enquête COVIREIVAC : les français et la vaccination | ORS Paca [Internet]. [cited 2021 Jun 30]. Available from: http://www.orspaca.org/notes-strategiques/enqu%C3%AAte-covireivac-les-fran%C3%A7ais-et-la-vaccination
8. Betsch C, Schmid P, Heinemeier D, Korn L, Holtmann C, Böhm R. Beyond confidence: Development of a measure assessing the 5C psychological antecedents of vaccination. PLoS One. 2018;13(12):e0208601.
9. Figueiredo A de, Simas C, Karafillakis E, Paterson P, Larson HJ. Mapping global trends in vaccine confidence and investigating barriers to vaccine uptake: a large-scale retrospective temporal modelling study. The Lancet. 2020 Sep 26;396(10255):898–908.
10. Yaqub O, Castle-Clarke S, Sevdalis N, Chataway J. Attitudes to vaccination: A critical review. Social Science & Medicine. 2014 Jul 1;112(Supplement C):1–11.
11. Nikolovski J, Koldijk M, Weverling GJ, Spertus J, Turakhia M, Saxon L, et al. Factors indicating intention to vaccinate with a COVID-19 vaccine among older U.S. adults. PLOS ONE. 2021 May 24;16(5):e0251963.
12. Detoc M, Bruel S, Frappe P, Tardy B, Botelho-Nevers E, Gagneux-Brunon A. Intention to participate in a COVID-19 vaccine clinical trial and to get vaccinated against COVID-19 in France during the pandemic. Vaccine. 2020 Oct 21;38(45):7002–6.
13. Bardenheier BH, Shefer A, McKibben L, Roberts H, Rhew D, Bratzler D. Factors predictive of increased influenza and pneumococcal vaccination coverage in long-term care facilities: the CMS-CDC standing orders program Project. J Am Med Dir Assoc. 2005 Oct;6(5):291–9.
14. Cannovo N, Scendoni R, Fede MM, Siotto F, Fedeli P, Cingolani M. Nursing Home and Vaccination Consent: The Italian Perspective. Vaccines (Basel). 2021 Apr 24;9(5):429.
15. Kohl-Heckl WK, Schröter M, Dobos G, Cramer H. Complementary medicine use and flu vaccination - A nationally representative survey of US adults. Vaccine. 2021 Sep 15;39(39):5635–40.
16. Ward JK, Alleaume C, Peretti-Watel P, Peretti-Watel P, Seror V, Cortaredona S, et al. The French public's attitudes to a future COVID-19 vaccine: The politicization of a public health issue. Social Science & Medicine. 2020 Nov 1;265:113414.

17. Smith DT, Attwell K, Evers U. Support for a COVID-19 vaccine mandate in the face of safety concerns and political affiliations: An Australian study. Politics. 2021 May 7;02633957211009066.
18. Verger P, Collange F, Fressard L, Bocquier A, Gautier A, Pulcini C, et al. Prevalence and correlates of vaccine hesitancy among general practitioners: a cross-sectional telephone survey in France, April to July 2014. Euro Surveill. 2016 Nov 24;21(47).
19. Glenton C, Carlsen B, Lewin S, Wennekes MD, Winje BA, Eilers R, et al. Healthcare workers' perceptions and experiences of communicating with people over 50 years of age about vaccination: a qualitative evidence synthesis. Cochrane Database Syst Rev. 2021 Jul 20;7:CD013706.
20. Wood S, Schulman K. When Vaccine Apathy, Not Hesitancy, Drives Vaccine Disinterest. JAMA [Internet]. 2021 Jun 2 [cited 2021 Jun 3]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2780792
21. TIP Tailoring Immunization Programmes (2019) [Internet]. [cited 2021 Nov 30]. Available from: https://www.euro.who.int/en/health-topics/disease-prevention/vaccines-and-immunization/publications/2019/tip-tailoring-immunization-programmes-2019
22. Catalogue of interventions addressing vaccine hesitancy [Internet]. [cited 2018 Nov 8]. Available from: https://ecdc.europa.eu/en/publications-data/catalogue-interventions-addressing-vaccine-hesitancy
23. Data for action: achieving high uptake of COVID-19 vaccines [Internet]. [cited 2021 Nov 30]. Available from: https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-vaccination-demand-planning-2021.1

Chapter 8

Systematic reviews and meta-analyses on clinical trials with vaccines for prophylactic use in old adults

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Introduction

Critically appraised literature, systematic reviews and meta-analyses on randomized clinical trials (RCTs) provide the highest level of scientific evidence for drug efficacy and safety, including vaccines. RCTs with prophylactic vaccines are more complex than the ones assessing therapeutic vaccines or drugs [1]. Vaccine assessment may need "challenge studies", with deliberate exposure of participants to infectious substances; the parallel development of immunological assays; the specificity of safety and efficacy endpoints and a fast track approval of new formulations addressing emergent variants of infectious agents.

The recruitment of adults older than 60 years in clinical trials with vaccines is of utmost importance. Immune responses in older adults may differ from younger people (see chapter 2) and the relative effects of vaccines in younger people (risk ratios, odds ratio) are indirect estimates of the relative effects in older people. Complications of infections (e.g. influenza or pneumococcal pneumonia) tend to be more common in older people. Thus, they may benefit from a larger absolute reduction in these complications from effective vaccines.

The exclusion of older persons from COVID-19 related trials, including COVID-19 vaccine trials, has been recently assessed. Of the 18 planned and active COVID-19 vaccine trials found in the clinicaltrials.gov database, between October 1, 2019 to June 1, 2020 [2], eleven trials (61%) included direct age-related exclusion criteria and the remaining 7 (39%) excluded participants with morbidities highly prevalent in the elderly. The authors concluded that older adults are likely to be excluded from 100% of COVID-19 vaccine trials [2]. Thus, the evidence that supports a clear benefit-risk of COVID-19 vaccination in old adults has been produced later on based in robust observational studies [3, 4].

The present work aims to investigate whether the exclusion of old adults from vaccine trials is common to other vaccines included in European national vaccination schedules (see chapter 1, reference n°5].

Specifically, we reviewed meta-analyses, systematic reviews and other primary studies that include the results (efficacy, effectiveness, and harm) of prophylactic vaccines obtained in clinical trials including old adults.

Methods

We conducted two separate searches illustrated in Figure 1. The first search aimed to identify studies which assessed the proportion of older adults (> 65 yo) included in vaccine trials. Eligible studies included reviews (systematic reviews, scoping reviews, overviews, narrative reviews) and primary studies (cross-sectionals or cohort studies of research studies). The second search aimed to identify systematic reviews of randomized trials assessing efficacy or safety of vaccines commonly recommended for older adults in European countries: influenza, herpes zoster, diphtheria, tetanus and pneumococcal infections.

The search adapted the recommendation proposed by Alper et al. [6]. Two independent reviewers searched for vaccine (August 31, 2021) in older adults or prevention in older adults in two different summaries (UpToDate and Dynamed) and extracted potentially relevant study titles from the reference lists. We then searched for studies in the following reference databases: ACCESSSS, TRIP Database, Cochrane Database of Systematic Reviews, Epistemonikos, Pubmed, Google Scholar. Only experimental studies, randomised controlled trials (RCTs) were included.

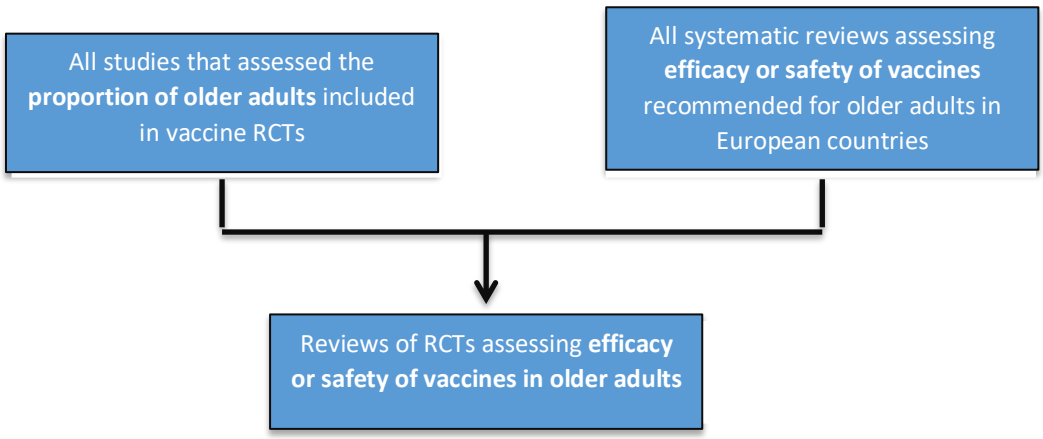

Figure 1. Flow chart of the search conducted in the study.

The indirectness of scientific evidence was categorized in four levels using the following criteria:

Level 1 - systematic review of RCTs recruiting only old adults;
Level 2 - systematic review of RCTs recruiting adults of all ages with subgroup analysis with at least one RCT including old adults;
Level 3 - systematic review of clinical trials in adults in which no RCT includes older adults;
Level 4 - absence of systematic review of RCT including old adults

Results

We found one study assessing demographic characteristics of participants in clinical trials with vaccines (any type). Among other variables, the study evaluated if clinical trials equitably represented individuals aged 65 years or older [7]. This cross-sectional study used data from completed interventional vaccine trials that were registered and reported on ClinicalTrials.gov (from July 1, 2011, to June 30, 2020) and excluded trials running outside the US. Among the 170 studies reporting age as a percentage, 12.1% (95% CI, 12.0%-12.3%) of participants were 65 years or older. They concluded that the older population are less frequently enrolled in trials than expected according to their representation in the US population, 16.0% [7]. We found direct evidence of vaccine effects in older people (level 1) for the influenza and the herpes zoster and 23-valent polysaccharide vaccines (PPV23). The best evidence for the effects of the 13-valent conjugate vaccine (PCV13) comes from a single RCT that include younger and older adults (level 2). We found no systematic review of randomized trials assessing the diphtheria or tetanus vaccines (level 4).

Diphtheria vaccines are based on diphtheria toxoid and became available in the 1940s. According to WHO [8] no controlled clinical trial of the efficacy of the toxoid in preventing diphtheria has ever been conducted. There is, however, strong evidence from observational studies to support the effectiveness of vaccination [8]. The efficacy of vaccines for preventing tetanus infections in older adults is well documented in several clinical trials but has never been addressed in systematic reviews. Two systematic reviews on the effects of vaccines in older adults for preventing influenza [9] and herpes zoster [10] were found and the results summarized in Table 1.

The evidence provided by the eight RCTs specifically designed to assess the effects of Influenza vaccine in the older population (level 1), demonstrates a lower incidence of the infection (or infection related) despite the low/moderate quality of the evidence [9]. There was not enough data about the effects on influenza complications. Data on adverse drug reactions for Influenza vaccine in older adults was not properly assessed in RCTs [9].

Altogether, the 24 RCTs conducted with the two herpes zoster vaccines- live zoster vaccine (LZV) and recombinant zoster vaccine (RZV), show that they are effective in preventing herpes zoster disease for up to three years (the main studies did not follow participants for more than three years) (Table 1) [10]. They also show that the vaccinated group had a higher incidence of adverse events, any systemic symptom and any local symptom, although most participants reported that their symptoms were of mild to moderate intensity [10]. Vaccine effects on zoster complications were not reported. Table 1 also includes the results of a systematic review that updates (from January 2016 to April 2019) the evidence base for efficacy and effectiveness of pneumococcal vaccines (PPV 23 and PCV13) against invasive pneumococcal disease and pneumonia in a general older population [11].

The evidence related to PPV 23 was based on 5 systematic reviews published previously and including a total of seven RCTs of PPV 23 vaccine in adult patients [12,13,14,15,16]. The update by Berild et al (2020) found no additional RCT [11] Of the 7 trials, the largest trial (n= 152,723) recruited young US military personnel, while the remaining 6 trials (accounting for 3,307 participants) recruited people aged 60 or older. Table 1 presents the overall results but the exclusion of younger participants influences the results of all-cause pneumonia significantly. The trial with younger participants did not have all-cause mortality as an outcome and the results including trials only with older participants were [RR] 0.80 [95% CI] (0.69-0.94), I^2 42%, and different from the 7 trials: [RR] 0.87 [95%CI] (0.76-0.98), I^2 43%. Concerning the 13-valent conjugate vaccine, PCV13, the update on Pneumococcal vaccines shows that only additional post hoc studies based on

the primary RCT, CAPITA, [17], and other observational, but not new RCTs were published [11]. The randomized placebo-controlled trial named CAPITA demonstrated the efficacy of PCV13 in adults aged ≥ 65 years. The study was conducted in the Netherlands, included almost 85,000 participants, and found a modified intention-to-treat vaccine efficacy of 37.7% [95% CI] (14.3-55.1) against the first episode of vaccine-type community acquired pneumococcal pneumonia and 75.8% [95% CI] (46.5-90.3) against the first episode of vaccine-type invasive pneumococcal disease [17]. No systematic reviews addressing the safety of pneumococcal vaccines in the older population were found.

The quality of the evidence (GRADE) reported in the systematic reviews referred in Table 1 varies according to the study and outcomes and goes from very low to high. The evidence coming from studies with influenza vaccines was graded as low and moderate [9] and that from herpes zoster studies as moderate [10]. The systematic review on PPV23 shows a huge variability in the quality of the evidence depending on the outcomes: high, for all causes of pneumonia and all causes of mortality and very low for pneumococcal pneumonia [11].

Type of vaccine and [study reference]	Search period	RCT (n)/subjects (n) condition/age	Outcomes (number RCT)	Results
INFLUENZA [9] Any	July 1, 2017 Europe; USA	8 RCTs/over 5000/>65	Efficacy (lab confirmed cases)	[RR] 0.42, [95%CI] (0.27 -0.66); 6%-2.4% NNT=30
			Effectiveness against influenza-like illness (8)	[RR] 0.59, [95%CI] (0.47 to 0.73); 6%-3.5%; NNT=42
			Safety (4)	Underpowered/lack of information
			Complications (4)	Underpowered/lack of information
HERPES ZOSTER [10] Live attenuated, LZV, single dose Adjuvanted recombinant subunit, RZV, two doses	Jannuary 31, 2019 Global	24 RCTs/88,531/>60	Effectiveness: incidence (24)	LZV [RR] 0.49, [95%CI] (0.43-0.56); 2%; NNT=50; RZV [RR] 0.08, [95%CI] (0.03-0.23); 3%; NNT=33;
PNEUMOCOCCAL [11]* 23-valent polysaccharide, PPV23	August 23, 2018 Global	**7** RCT 596 COPD/ 61-73 167 CLD/40-80 778 >65 1006/55-105 691 CAP history/50-85 152723 healthy /17-20 49 COPD/47-86	PPV23 effectiveness: All-cause pneumonia (7) Pneumococcal pneumonia (3) Mortality due to pneumonia (4) All-cause mortality (7)	PPV23, all-cause pneumonia [RR] 0.87, [95%CI] (0.76–0.98) I(2) = 43% Pneumococcal pneumonia [RR] 0.54, [95%CI] 0.18-1.65, p=0.01, I(2)=77% Mortality due to pneumonia [RR] 0.67, [95%CI] 0.43-1.04, p=0.67, I(2)=0% All-cause mortality RR] 1.04, [95%CI] 0.87-1.24, p=0.95, I(2)=0%
RCT: Randomized Clinical Trial; COPD: Chronic Obstructive Pulmonary Disease; CLD: Chronic Lung Disease; CAP: Community Acquired Pneumococcal Pneumonia; NNT: number needed to treat. * For 13-valent conjugated, PCV13 vaccine there are no RCT other than the original CAPITA study, see text .				

Table 1. Systematic reviews on the effects of vaccines in the elderly obtained from Randomized Clinical Trials

Summary and conclusions

The exclusion of old adults, reported for RCTs with COVID-19 vaccines, does not occur with vaccines to prevent influenza, herpes zoster and pneumococcal diseases. There are RCTs assessing the efficacy/effectiveness of these vaccines in the older population. However, the overall quality of the evidence provided by these RCTs has been graded as moderate in the systematic reviews mainly because age was not a discriminator in vaccine trials, the comorbidities highly prevalent in the older population and other bias were not properly addressed, and the outcomes are different among trials. As expected, the evidence coming from RCTs is absent for the older vaccine to prevent diphtheria in adults (any age). The well-established benefit-risk of this vaccine in the eradication of the disease justifies why no clinical trials controlled with placebo exist. Several RCTs with tetanus vaccines showed its efficacy but we did not find a systematic review that assessed their risk of bias or synthesised their results, probably because there are several combinations of different vaccines including tetanus that limit data aggregation and comparisons. The gaps in experimental studies specifically addressing adverse effects of vaccines in the older population are partially mitigated, in

the European context, by a strong Pharmacovigilance supranational system under the supervision of the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency's (EMA).

In general, the older population are underrepresented in RCTs with vaccines. Trials assessing the efficacy of vaccines in older adults may not be a priority when there are RCTs in younger adults showing benefits in patient outcomes and good quality observational studies documenting that the efficacy can be extrapolated for older populations. However, there is plenty of room to improve the inclusion criteria related to comorbidities highly prevalent in older adults' outcomes and other confounding factors in order to increase the quality of the evidence supporting the use of prophylactic vaccines in the older population. For this purpose, European policies to ensure that old adults are properly represented in the clinical trials with vaccines are needed.

References

1. https://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf. Accessed on september 16, 2021
2. Helfand BKI, Webb M, Gartaganis SL, Fuller L, Kwon C, Inouye SK. The Exclusion of Older Persons From Vaccine and Treatment Trials for Coronavirus Disease 2019—Missing the Target. JAMA Intern Med. 2020;180(11):1546–1549. doi:10.1001/jamainternmed.2020.5084
3. https://ansm.sante.fr/actualites/les-vaccins-reduisent-fortement-le-risque-de-forme-grave-de-covid-19-chez-les-personnes-de-plus-de-75-ans-en-france. Accessed on december 17, 2021
4. Jabagi MJ, Botton J, Bertrand M, Weill A, Farrington P, Zureik M, Dray-Spira R. Myocardial Infarction, Stroke, and Pulmonary Embolism After BNT162b2 mRNA COVID-19 Vaccine in People Aged 75 Years or Older. JAMA 2021; Nov 22;e2121699. doi: 10.1001/jama.2021.21699.
5. https://vaccine-schedule.ecdc.europa.eu/. Accessed on september 10, 2021
6. Alper BS, Haynes RB. EBHC pyramid 5.0 for accessing preappraised evidence and guidance. BMJ Evidence-Based Medicine. 2016 Aug 1;21(4):123–5.
7. Flores LE, Frontera WR, Andrasik MP, et al. Assessment of the Inclusion of Racial/Ethnic Minority, Female, and Older Individuals in Vaccine Clinical Trials. JAMA Netw Open. 2021;4(2):e2037640. doi:10.1001/jamanetworkopen.2020.37640
8. https://www.who.int/immunization/sage/meetings/2017/april/2_Review_Diphtheria_results_April 2017_final_clean.pdf. Accessed in September 10, 2021
9. Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, Rivetti A. Vaccines for preventing influenza in the elderly. Cochrane Database of Systematic Reviews 2018, Issue 2. Art. No.: CD004876. DOI: 10.1002/14651858.CD004876.pub4. Accessed 30 August 2021.
10. Gagliardi AMZ, Andriolo BNG, Torloni MR, Soares BGO, de Oliveira Gomes J, Andriolo RB, Canteiro Cruz E. Vaccines for preventing herpes zoster in older adults. Cochrane Database of Systematic Reviews 2019, Issue 11. Art. No.: CD008858. DOI: 10.1002/14651858.CD008858.pub4. Accessed 30 August 2021.
11. Berild JD, Winje BA, Vestrheim DF, Slotved HC, Valentiner-Branth P, Roth A, Storsäter J. A Systematic Review of Studies Published between 2016 and 2019 on the Effectiveness and Efficacy of Pneumococcal Vaccination on Pneumonia and Invasive Pneumococcal Disease in an Elderly Population. Pathogens. 2020 Apr 3;9(4):259. doi: 10.3390/pathogens9040259.

12. Diao, W.Q.; Shen, N.; Yu, P.X.; Liu, B.B.; 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, 1496–1503.
13. 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, e0169368.
14. 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, 1540–1550, Corrigendum in 2016, 34, 4083–4084, doi:10.1016/j.vaccine.2016.06.045.
15. Schiner-Rohe, J.; Witt, A.; Hemmerling, J.; von Ei, C.; Leverkus, F.W. Efficacy of PPV23 in Preventing Pneumococcal Pneumonia in Adults at Increased Risk—A Systematic Review and Meta-Analysis. PLoS ONE 2016, 11, e0146338.
16. Tin Tin Htar, M.; Stuurman, A.L.; Ferreira, G.; Alicino, C.; Bollaerts, K.; Paganino, C.; Reinert, R.R.; Schmitt, H.J.; Trucchi, C.; Vestraeten, T.; et al. Effectiveness of pneumococcal vaccines in preventing pneumonia in adults, a systematic review and meta-analyses of observational studies. PLoS ONE 2017, 12, e0177985.
17. Bonten, M.J.; Huijts, S.M.; Bolkenbaas, M.; Webber, C.; Patterson, S.; Gault, S.; van Werkhoven, C.H.; van Deursen, A.M.; Sanders, E.A.; Verheij, T.J.; et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N. Engl. J. Med. 2015, 372, 1114–1125.

Chapter 9

Conclusions and Recommendations

Life expectancy at retirement in most European countries exceeds more than 2 decades and can even last 3 to 4 decades in some individuals. During this period, there is generally a decline of the immune system and host defense mechanisms, which are exacerbated by the presence of comorbidity. In view of the burden of vaccine preventable infectious diseases (VPIDs) in the old population, it is evident that there is a need to harmonize vaccination programmes in adults over 65 years to favour healthy ageing by bridging the existing adult vaccine gap and protecting the old at-risk population.

Observational studies have demonstrated that response to vaccines in old age is mostly good. Furthermore, lipid-based adjuvants are extremely potent in old age. mRNA COVID-19 vaccines provide adequate protection in ageing patients, although the responses appear to be waning sooner. This tells that it is now possible to develop new generation of vaccines which will better protect most old individuals, even in the force of comorbidity.

The main problem of immunization in the older population and high-risk old adults is too low vaccine coverage rates. This can be explained by several considerations. The general perception is that vaccination is for children and not adults. This perception needs to be ameliorated by public health education of the older population and their careers. There may also be fear of adverse side effects. Even in these populations, vaccine benefits largely overcome risks.

Too often in the public, the positive effects of vaccine are restricted to their specific anti-infectious effect. It is now demonstrated that vaccines targeting specifically flu, pneumococcal disease and herpes zoster have also been associated with protective effects on cardio- and neuro-vascular diseases. Moreover, infants/young adults pertussis and diphtheria vaccines might have any longer-term neuro-inflammation protective impacts. That is to say that immunization in old adults, especially when integrated in a life course program, is extremely significant for health.

In addition to the protection for the individuals, herd immunity obtained by vaccines allows protection for the community. In a world which is quickly changing, data following the introduction of conjugate pneumococcal vaccines 13 (PVC 13) showed that vaccines are highly likely to limit evolution of anti-microbial resistance.

In a such complex and scalable context, it appears essential to insist on the importance of proposing harmonized adult vaccination programme. Such science-based vaccine initiative could favour healthy aging, protect old adults with comorbidity and finally reduce health care use of expenditures.

1) Recommendations for promoting "health ageing"

Essential vaccines for adults over 65

Flu vaccine: annual vaccination with current annually determined vaccines and adjuvants. Further research is needed to identify a pan influenza strain protective vaccine
Pneumococcal vaccines: vaccination with vaccines which cover the most numerous Pneumococcal serotypes (PPV23 and PCV20)
COVID vaccine: during the COVID pandemic with mRNA vaccines
Tetanus vaccine: particularly in adults at risk of skin injuries to be renewed every 10 years
Pertussis vaccine: for adults with grand children or in regular contact with young children, with booster every 10 years
Herpes Zoster vaccines for all adults (above 50 years and above 18 years at increased risk of herpes zoster) with the new and particularly effective adjuvanted recombinant subunit vaccine.

Specific vaccine indications

Hepatitis B vaccine: the new vaccines with novel adjuvants are extremely protective in old adults living in community
Travel-specific vaccines as indicated (including yellow fever, hepatitis, meningococcal meningitis, typhoid fever, cholera, poliomyelitis, rabies, Japanese encephalitis, tick-borne encephalitis, and dengue)

Implementation of a European electronic data system - similar to the Adult Immunization Status (AIS) in the US - that tracks the percentage of members 19 years of age and older who are up to date on recommended routine vaccines for influenza, tetanus and diphtheria (Td) or tetanus, diphtheria and acellular pertussis (Tdap), zoster and pneumococcal.

2) Vaccines recommendations for old people with comorbidity

Because immune responses are inherently time-dependent processes, immune function will inevitably change with ageing. Pathological processes are superimposed on this chronological framework explaining that immune impairments vary between individuals of the same age and cannot currently be reliably predicted by any specific marker. Approaches to accommodate this global deficit might include vaccines with adjuvant activity, to overcome higher thresholds for activation, vaccines with different antigenic loads, and vaccines with different delivery routes or dosing intervals.

Old patients with diabetes: High quality randomized controlled clinical trials and systematic reviews conclude that influenza vaccination in old diabetic patients is effective based on influenza morbidity and mortality as outcome parameters.

Old adults suffering from impaired kidney function and or benefiting of dialysis: The effectiveness of influenza and pneumococcal vaccines is impaired in these patients. Indeed the proportion of responders to Hepatitis B vaccine containing potent lipid-based adjuvant is higher. Vaccination with an mRNA vaccine

against COVID-19 also appears to result in very low responses in kidney transplant recipients and suboptimal responses in dialysis patients.

Vulnerable or immunocompromised old adults: Immune-compromised patients may have a higher incidence of vaccine-preventable diseases and a more severe form of any infectious diseases. Few studies have been done on vaccine responses in immunocompromised patients or with corticosteroids as the single treatment, and it is often difficult to discern the indipendent effect of the underlying illness. In a review on influenza vaccination, the effects were found to be controversial, ranging from a normal serological response to impared responses. For COVID vaccines, questions currently exist regarding the utility of measuring antibody levels after vaccination, providing a vaccine boost dose and further repeat doses, for all people but especially for vulnerable people.

The impact of comorbidity on the immune aging process appears more and more clearly. In future vaccine trails in the old population more detailed investigations on comorbidity and immunotherapy need to be included for allowing establishing clear vaccine policy.

3) Vaccination schedules in EU countries and education

The brief survey presented in this paper demonstrates considerable variation in vaccination schedules recommended for old people in different EU Member States. Whilst it is clear that individual Member States have their own powers to recommend and facilitate vaccination, there are benefits of a unified recommendation. This would facilitate clarity, movement of individuals between countries and enable the supply chain to work better.

A degree of confusion exists in the old population concerning the health benefits of vaccination and the schedules of vaccination. Education of the older population and their careers is crucial in this regard. Such education through public health systems, geriatricians and general practitioners must be improved and maintained.

Future development in immune protection

The use of vaccination to stimulate protective immune responses is recognised across all age groups. Research has continued to refine vaccines and develop molecular approaches and technology for human use. Classic examples are the use of recombinant proteins and the development of mRNA vaccines both of which have been successfully used over the whole age range including old age. However, as described in the chapters above, the presence of multimorbidity and immunosuppressive therapies (e.g., chemotherapy for malignant disease) may considerably reduce the contrived immune response and therefore protection offered by vaccines. Opportunities now exist and will likely be further expanded to utilize passive contrivance of immunity by administration of antibodies both polyclonal and monoclonal to evoke protection. For example, it has already been demonstrated that administration of specific monoclonal antibodies to individuals with compromised immunity exerts strong, specific protection against the pathogen to which it is directed. This approach has been successfully demonstrated for SARS COV2 in protection of immuno-compromised people. While such therapy is expensive, further developments in technology and chemistry are anticipated and likely to considerably reduce costs and therefore increase availability. In addition, short term protection against some viral infections could be considered using such an approach.

Working Group composition and procedures

The project proposal was discussed and approved by the FEAM Council in May 2021. The report was prepared by consultation with a Working Group of experts acting in an individual capacity:

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The Working Group met in May, July, October and November 2021 by videoconference. In addition to the Working Group meetings, evidence was gathered in a workshop organised by the FEAM European Biomedical Policy Forum (October 2021). The draft report was reviewed and endorsed by the 23 FEAM academies in January 2022. FEAM thanks all who contributed to preparing and reviewing the text.

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