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Preface

Demographic changes lead to an increase in the number and percentage of older persons worldwide. It is estimated that by 2080 the median age of the population in Europe will increase by 4.2 years, and the proportion of older persons (>65 years) will increase from 19.2 to 29.1% during this time. The proportion of the very old (>80 years) will increase even more, from 5.4 to 12.4%. In view of these developments, it is of utmost importance to the individual person as well as to society as a whole to promote healthy aging and ensure quality of life for the older population.

Many infectious diseases show increased incidence and severity with age. In addition to the acute event of infection, which is often associated with high morbidity and mortality in older age groups, there can be severe additional, often long-term consequences. Exacerbations of underlying chronic diseases during or shortly after infections are frequent, and many older patients will not recover fully after serious infections. In the worst-case scenario, this leads to a loss of independence, which might necessitate admission to long-term care. Vaccines are the most efficient strategy to prevent infectious diseases, and the tremendous success of childhood vaccination programs in reducing the burden of many infectious diseases worldwide is undisputed. Prevention of infections affecting the older population by vaccination is an important measure to achieve the overall goal of promoting health in this age group.

This book summarizes age-related changes of the immune system and their impact on immune responses to vaccination, as well as other factors influencing vaccine-induced immune responses in old age. It gives an overview of vaccines which are currently available for older adults and of novel technologies and targets which hopefully will lead to more and improved vaccines for this vulnerable population.

The immune system is a complex network of different cell types and soluble factors, with intricate interactions not only amongst its components but also with the rest of the body. The innate immune system consists of several cell types with distinct roles in early immune responses and antigen presentation. Alterations in receptor expression, signaling, transcriptional programming and cytokine production and responsiveness are contributing to age-related functional defects in neutrophils, monocytes/macrophages and dendritic cells. Natural killer cells, which recognize and eliminate infected and tumor

cells, show age-related changes in their phenotype and subset composition as well as their functions, which includes cytotoxicity and cytokine production. The aged adaptive immune system is characterized by a diminished repertoire and diversity. Age-associated changes in hematopoiesis and involution of the thymus lead to decreased output of newly generated naïve T cells. At the same time, antigen-experienced T cells, and particularly highly differentiated effector T cells accumulate. Signaling defects, limited proliferative capacity of exhausted or senescent-like T cells, and alterations in cytokine production contribute to decreased T cell function in old age. The output of naïve B cells is also decreased, and the composition of the B cell compartment changes with age. Intrinsic defects of B cells as well as age-related changes of other cell types interacting with B cells, particularly T helper cells, contribute to decreased production of specific antibodies upon antigenic challenge. At the same time, increased frequencies of autoreactive antibodies can be observed in old age. Metabolic changes have been described for many immune cell types and their relevance for immunological functions is more and more recognized in the field. A chronic subclinical inflammatory status has been observed in older adults, which can be attributed to altered cytokine production by innate and adaptive immune cells, as well as other cell types, such as adipocytes, fibroblasts, and many others. In addition to its impact on the regulation of immune responses, this inflammatory background has been described to contribute to many age-associated diseases, such as e.g. atherosclerosis and neurodegeneration.

Age-related changes of the immune system have a direct impact on vaccine-induced immune responses. Innate immune cells recognize vaccine components (antigens and adjuvants) at the site of injection and elicit a local inflammatory response. Antigens are taken up by phagocytes and are presented to T cells. Adaptive immune responses in the lymph nodes involve myeloid cells, as well as T cells and B cells. In most cases, antibody concentrations are measured to determine immunogenicity of a vaccine. It has to be taken into account that T cell help is crucial for optimal antibody production and that T cells also play an important role in conferring protection from many infectious diseases. In addition, other factors such as underlying chronic diseases, which are highly prevalent in the older population, and frailty negatively influence vaccine-induced immune responses. The influence of adipose tissue on immune responses needs be considered, and research in this area has expanded over the last years, particularly in view of an increasing prevalence of obesity.

Many countries have specific vaccine recommendations in place for older adults. Vaccination against influenza and pneumococcal disease is advocated throughout Europe. An increasing number of countries also include vaccination against herpes zoster in their recommendations. Antibody responses following influenza and pneumococcal vaccination are generally lower in older compared to younger adults. Various strategies have been employed to improve immunogenicity of influenza vaccines including higher antigen content, alternative administration routes and adjuvants, generally leading to slightly higher antibody responses. It has to be taken into account that antibodies might not be the only mechanism conferring protection. Over the last year vaccine-induced T cell re-

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sponses have been studied in more detail. However, large-scale clinical trials still rely mainly on antibody-related parameters as measurement of T cell responses is technically more complex and therefore difficult for large sample numbers. Protection of the older population against pneumococcal disease remains a challenge. Vaccination of children with conjugated pneumococcal vaccines provides some protection of the older population via herd immunity effects, but vaccination of older adults offers more direct protection. A 23-valent polysaccharide vaccine and a 13-valent conjugate vaccine are currently available for the older population but have limitations, such as relatively short-lived protection and the restricted serotype coverage. Several countries recommend sequential vaccination with the conjugate and then the polysaccharide vaccine in order to combine benefits from both vaccine types. For both influenza and *Streptococcus pneumoniae*, efforts to develop "universal" vaccines containing conserved antigens, which would cover many or all strains or serotypes, respectively, are ongoing. This strategy could overcome current limitations, such as the need for annual re-vaccination against influenza and serotype replacement for *S. pneumoniae*. A first live-attenuated vaccine against herpes zoster was recently replaced by a recombinant vaccine containing the viral glycoprotein gE and the adjuvant AS01B. The efficacy of the recombinant vaccine is high and in contrast to many other vaccines similar for all age groups, including the very old. In contrast to the live-attenuated vaccine, this vaccine can also be used in immunocompromised persons, which are also at a very high risk of developing herpes zoster. Prevention of herpes zoster is of particular importance as postherpetic neuralgia, a frequent complication leading to long-term severe, hardly treatable neuropathic pain, dramatically impacts the quality of life of affected patients and frequently leads to loss of independence.

In addition, vaccines which are administered to adults of all age groups, e.g. against tetanus and diphtheria, also need to be considered in the context of aging. Tetanus- and even more so diphtheria-specific antibody concentrations decline with age, and regular vaccinations throughout adulthood are important to ensure protection also in older age. The levels of vaccination coverage and protective antibody levels vary greatly between different countries, e.g. within Europe. As many older adults are still healthy and very active, travelling to exotic destinations has become more popular among the older population. Adequate medical preparation and advice is crucial for these travelers. Besides management of underlying chronic conditions, administration of vaccines relevant for the destination and travel style is essential. In addition to classical travel vaccines, also "routine" vaccines for this age groups need to be reviewed and completed, if necessary. It has to be considered that older travelers might not respond adequately to neo-antigens and that immune responses are frequently developing slower in older adults.

There are still many pathogens which cause significant morbidity and mortality in the older population but for which vaccines are currently not available. Respiratory syncytial virus (RSV) can cause severe lower respiratory tract infections in infants, immunocompromised patients, and older adults, and vaccine development for this pathogen has been ongoing for decades. Several recent vaccine candidates have been shown to be safe and immunogenic but failed to confer protection against disease in clinical trials enrolling

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older adults. Recent advances in the structural biology of RSV proteins and a better understanding regarding the immune responses needed for protection might provide opportunities for the development of novel vaccine candidates. Nosocomial infections are frequent in the older population, and many of the bacterial nosocomial pathogens show increasing rates of antibiotic resistance. Vaccines against these pathogens are highly desirable, and important progress has been made in vaccine development, e.g. against *Clostridium difficile* and *Staphylococcus aureus*. There is still a plethora of microorganisms (bacterial, viral, and fungal), which are particularly pathogenic for older adults, and preclinical as we well as clinical vaccine development is ongoing for many of them. For several decades, vaccine development has been driven by the need to prevent infectious diseases in childhood. Awareness that vaccines developed for children might not be optimal for adults, and particularly for the older population has only arisen in the recent past. Novel vaccine, adjuvant, and administration strategies should also be tested in older adults. Approaches which specifically target the aged immune system and are able to overcome its limitations have great potential to provide protection from various pathogens. Scientific progress in understanding the details of immunosenescence is the basis for the development of such strategies. However, in order to exploit their full protective potential, it is essential to improve vaccine uptake throughout adulthood and particularly in the older population. Information and education of stakeholders, healthcare professionals, and the general public are important in order to increase awareness of vaccines and to overcome vaccine hesitancy. In addition, easy access – logistical and financial – to vaccines and vaccination for everyone needs to be ensured to reach vaccine uptake goals.

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