With increasing age, the human immune system undergoes characteristic changes, termed immunosenescence, which lead to increased incidence and severity of infectious diseases and to insufficient protection following vaccination. Functional defects and altered frequencies of innate and adaptive immune cells impair local responses at the site of vaccine injection, hamper the generation of primary responses to neoantigens, prevent the effective induction of memory lymphocytes, and decrease the effect of booster vaccination. As a result, antibody responses of elderly vaccinees are weaker and decline faster, and long-term protective effects of vaccination cannot be taken for granted in elderly persons. Improved vaccination strategies, new adjuvants, and new vaccines that specifically target the aged immune system will help to overcome the limitations of immunosenescence and ensure a better protection of the vulnerable elderly population.

In recent decades, progress in health care, the advent of antibiotics and vaccination, and improved life standards have led to a dramatically increased lifespan. The demographic changes associated with these developments challenge the health care and social systems of all developed countries. It has been predicted that by 2050, almost 40% of the European and US population will be >60 years old [1]. With this perspective, public and scientific interest in age-related diseases and strategies to improve the quality of life of the elderly population is continuously growing.

One major health issue arising with age is the increasing prevalence and severity of some infectious diseases, which partly reflects the age-related decline in immune function. Pneumonia, infections of the urinary tract and the skin, and reactivation of infection with latent pathogens, such as varicella zoster virus and Mycobacterium tuberculosis, are common in the elderly population. Influenza, for example, is often associated with severe complications and secondary infections in elderly persons. During an epidemic influenza season, 3–5 million cases of severe disease and 250,000–500,000 deaths occur worldwide [2]. In industrialized countries, most deaths associated with influenza occur among elderly persons. In developed countries, such as the United States, deaths due to pneumonia and influenza account for >3% of all deaths in people aged ≥65 years [3]. Vaccination is of crucial importance in preventing infection and protecting the vulnerable elderly population from disease. Because the efficacy of a vaccine depends on the quality of the immune response, immunocompromised persons, such as very young infants and elderly persons, are likely to be insufficiently protected [4]. Thus, over the past decade, a large number of studies have shown that a variety of vaccines are less efficient in elderly persons. Annual vaccination against influenza, for example, is recommended in most developed countries for persons with underlying chronic diseases and for everybody aged >60 or >65 years, depending on individual national recommendations. However, antibody responses after vaccination are lower in elderly persons than in young adults [5]. Decreased IgA and IgG antibody concentrations, delayed peak antibody titers, and a faster decline in titers occur, especially in very old and frail persons. For example, seroprotection against influenza virus strains is only 29%–46% in persons aged ≥75 years, compared with 41%–58% in persons 60–74 years of age (table 1). Because nonadjuvanted influenza virus subunit vaccines show lower seroprotection and seroconversion rates than do adjuvanted subunit, virosomal, or split vaccines [14, 15], they should not be administered to elderly persons. There are >90 serotypes of Streptococcus pneumoniae, and many of these frequently affect young children and elderly persons. Fifteen percent to 30% of cases of pneumonia are associated with invasive pneumococcal disease (e.g., bacteremia or meningitis), with a case-fatality rate of up to 40% for persons aged ≥85 years [10]. Currently, the 23-valent pneumococcal polysaccharide vaccine offers protection against
Table 1. Vaccines and their efficacy in elderly persons.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Vaccine type</th>
<th>Vaccine efficacy in elderly persons, %</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>Inactivated virus, subunit, adjuvanted subunit, and virosome</td>
<td>55 (32)a</td>
<td>[5]</td>
</tr>
<tr>
<td></td>
<td>A/H3N2 Inactivated virus, subunit, adjuvanted subunit, and virosome</td>
<td>58 (46)a</td>
<td>[5]</td>
</tr>
<tr>
<td></td>
<td>B Inactivated virus, subunit, adjuvanted subunit, and virosome</td>
<td>41 (29)a</td>
<td>[5]</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Inactivated virus</td>
<td>63b</td>
<td>[6]</td>
</tr>
<tr>
<td></td>
<td>A Virosome</td>
<td>65 (97)c</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>B Subunit</td>
<td>33b</td>
<td>[6]</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Live attenuated virus</td>
<td>64 (18)d</td>
<td>[8]</td>
</tr>
<tr>
<td>Pertussis</td>
<td>Toxoid and acellular components</td>
<td>&gt;81e</td>
<td>[9]</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Nonconjugated polysaccharide</td>
<td>50–70f</td>
<td>[10]</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>Inactivated virus</td>
<td>99g</td>
<td>[9]</td>
</tr>
<tr>
<td>Tetanus and diphtheria</td>
<td>Toxoid</td>
<td>99 and 84h</td>
<td>[9]</td>
</tr>
<tr>
<td>Tickborne encephalitis</td>
<td>Inactivated virus</td>
<td>70f</td>
<td>[11]</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Live attenuated virus</td>
<td>100</td>
<td>[12, 13]</td>
</tr>
</tbody>
</table>

**NOTE.** VIEU, Vienna units.

- a Seroprotection of persons aged 65–74 years (>75 years).
- b Seroprotection (anti-hepatitis A virus concentration >20 IU/L; anti-hepatitis B surface antigen concentration of >10 IU/L) of persons aged ≥80 years after 2 booster vaccinations.
- c Seroprotection (>20 IU/L) of persons aged ≥50 years after primary vaccination (after booster vaccination).
- d Vaccine efficacy in persons aged 60–69 years (>80 years old).
- e Elderly persons (median age, 66 years) with protective antibody levels against pertussis after vaccination with low-dose diphtheria, tetanus, pertussis, and inactivated poliovirus vaccine.
- f Vaccine efficacy in the general elderly population regarding invasive pneumococcal disease.
- g Vaccine efficacy in elderly persons (median age, 66 years) after booster vaccination with low-dose diphtheria, tetanus, pertussis, and inactivated poliovirus vaccine.
- h Elderly persons (median age, 66 years) with protective antibody levels against tetanus and diphtheria after booster vaccination with low-dose diphtheria, tetanus, pertussis, and inactivated poliovirus vaccine.
- i Elderly persons (>60 years) with protective antibody levels (>100 VIEU/mL) against tickborne encephalitis after booster vaccination 3–4 years after the last vaccination.

invasive pneumococcal disease (50%–70%) in the general elderly population but has only moderate effects (20%) in the high-risk elderly population [16]. Moreover, the vaccine has only little effect against pneumonia. Although 7-valent conjugate polysaccharide vaccines have been developed that improve vaccine responses in young children, these vaccines failed to improve immunogenicity in elderly persons [17].

Herpes zoster, which is caused by reactivation of the varicella-zoster virus, is another disease that predominantly occurs in elderly persons. A live attenuated virus vaccine aiming to prevent herpes zoster and postherpetic neuralgia has recently been introduced. Although vaccine efficacy is ~64% in the elderly population, only 18% of persons aged ≥80 years are protected [8]. Because of increased travel activity of elderly persons, travel vaccination has become an increasingly important issue. For example, vaccination against hepatitis A induces protective antibody responses in only 63% of elderly vaccinees, compared with 92% of young adults [6]. Another travel vaccine aims to protect against yellow fever, which is endemic in tropical regions of Africa and South America. With the recent increase in the administration of yellow fever vaccine to elderly persons, advanced age has been suggested to be a risk factor for adverse effects [18]. Moreover, booster vaccinations against tetanus, tickborne encephalitis, pertussis, and diphtheria induce a decreased response and have a shortened duration of protection in healthy elderly persons (table 1) [9, 11].

**THE IMMUNE RESPONSE FOLLOWING VACCINATION**

Vaccines induce both innate (nonspecific) and adaptive (specific) immune responses. Figure 1 schematically depicts the immune responses induced by vaccination and indicates possible age-related alterations. Protein antigens are usually injected together with adjuvants such as aluminum salts. Adjuvants retain antigen at the site of injection and/or stimulate local innate immune responses, such as the production of pro-inflammatory cytokines by macrophages [20]. This provides a “danger” signal [21] that supports the maturation of dendritic cells. The antigen is taken up by macrophages or dendritic cells. Dendritic cells are then activated and migrate to regional lymph nodes, where they present the processed antigen on their surface together with major histocompatibility complex (MHC) molecules. Inactivated vaccines are presented in the context of
Figure 1. Schematic representation of the immune response and its age-related alterations following vaccination. Protein antigens administered together with adjuvants induce the activations of innate immune responses at the site of injection. The antigen is taken up by antigen-presenting cells (1), such as macrophages and dendritic cells (DCs). The local innate immune response facilitates maturation of DCs, which present stable major histocompatibility complex/peptide complexes (2). Mature DCs migrate into lymph nodes (3), where they induce activation and clonal expansion of naïve CD4+ (4) and CD8+ (5) T cells. The activation and differentiation of naïve B cells is induced by antigen and CD4+ T cell help (6). Naïve B cells differentiate into memory B cells and antibody-secreting B cells (7). Long-term immunity is assured by memory B and T cells in the blood and lymph nodes, as well as by long-lived plasma cells and memory T cells in the bone marrow [19].
MHC class II molecules to CD4+ T lymphocytes. Vaccination with live attenuated vaccines can lead to the intracellular production of antigenic peptides within antigen-presenting cells, which are then presented to CD8+ T lymphocytes in the context of MHC class I molecules. T cells recognize the MHC/antigen complex with their specific T cell receptors. This leads to T cell activation, clonal expansion of effector T cells, and the formation of long-lived memory T cells, the hallmark of adaptive immunity. In the case of primary exposure to an antigen, naive, antigen-inexperienced T cells are activated. On booster vaccination, preexisting memory T cells recognize antigen-loaded dendritic cells, expand rapidly, and differentiate into effector T cells, which leads to a faster and stronger memory response. CD4+ T helper cells stimulate B cells that have been activated by contact with their specific antigens to differentiate into memory B cells and antibody-secreting B cells, which migrate to the periphery. These B cells have undergone recombination events that facilitate the expression of IgG instead of IgM antibodies, the so-called “heavy-chain isotype switching.” Some of these B cells further differentiate into long-lived plasma cells that reside in the bone marrow. Antibodies circulate in the blood and enter the mucosa, where they directly bind pathogens, preventing entry into host cells and enhancing recognition by phagocytes. As is the case with memory T cells, memory B cells are capable of mounting fast and strong responses to secondary vaccination.

Antigens that have highly repetitive structures, such as bacterial polysaccharides, are capable of inducing antibody responses without the need for T cell help [22]. Mature B cells directly bind repetitive elements of these antigens, which are either cell bound or soluble, via membrane-bound antibodies. Antigen-induced activation leads to differentiation into antibody-producing B cells that migrate to the periphery without the need for T cell help. Generally, T cell–independent antibody responses are only short-lasting, because differentiation into long-lived plasma cells is not induced. They have low affinity because of reduced antibody class switching to IgG and do not induce immunologic memory. However, some T cell–independent antigens, such as the polysaccharide vaccine against S. pneumoniae, are believed to induce long-lived protective immunity. The underlying mechanisms are unclear. It has been speculated that antigens might persist for long periods in lymphoid tissue in cells such as follicular dendritic cells, where they continuously stimulate B cells.

AG E-RELATED CHANGES OF THE IMMUNE SYSTEM AND THEIR IMPACT ON VACCINATION

Declining immune function with age substantially contributes to the decreased efficacy of vaccines in elderly persons. The underlying complex changes in the immune system are collectively termed immunosenescence, and they affect cell types of both the innate and the adaptive immune system.

The innate immune response in old age. Neutrophils and macrophages have a reduced phagocytic capacity, and their oxidative burst is decreased in elderly persons [23]. Additionally, the up-regulation of MHC class II expression is impaired in old macrophages [24]. Phagocytic cells recognize common structures of pathogens via Toll-like receptors (TLRs). TLR signaling leads to the efficient activation of the phagocytes and induces innate immune responses. Defects in the expression of TLRs have been shown in macrophages of elderly persons [25]. The number of Langerhans’ cells in the skin also decreases with age, and the expression of MHC class I and II, as well as the capacity to present antigen, are reduced in dendritic cells from old mice [26]. All of these age-related impairments of the innate immune response can hamper the success of vaccination by decreased uptake of antigen at the site of injection, resulting from reduced phagocytosis. Defects in the processing and presentation of antigens lead to diminished activation and stimulation of adaptive immune cells.

Despite functional defects in innate immune cells on a per-cell basis, inflammatory processes occur ubiquitously with increasing age. This characteristic subclinical proinflammatory status has been termed “inflamming” [27] and is known to be a predisposing factor for age-related diseases. Proinflammatory cytokines, such as IL-6, IL-1β, and TNF-α, are produced at elevated levels in elderly persons in locations including the brain, blood vessels, and bones. “Inflamming” is believed to be due to chronic stimulation of innate immunity by products of degradation processes and/or by the partial inability of the aged immune system to eliminate some pathogens, which may lead to chronic yet inefficient innate immune responses.

These persistent inflammatory processes may hamper the aged organism’s capacity to recognize stimuli induced by pathogens or vaccines as “danger” signals. Signals of higher intensity than operative in young persons may be needed to induce dendritic cell maturation and adaptive immunity. Conventional vaccines and adjuvants may fail to reach this critical threshold at the site of injection in elderly persons. Improved antigen delivery systems (e.g., liposomes and virosomes); immunostimulatory adjuvants, such as saponins, adjuvants targeting TLRs (e.g., 3-deacetylated monophosphoryl lipid A and CpG-oligodeoxynucleotides), and nanoparticles [28]; or the administration of recombinant cytokines might help to overcome these limitations. At present, only 2 influenza vaccines containing new adjuvants are registered in Europe. One vaccine contains a virosomal formulation of influenza antigens, whereas the other one uses an oil-in-water emulsion of saporin and other components (MF59).

The adaptive immune response in old age. One of the most prominent events during aging is the continuous loss of thymic
cortex and medulla, which starts already very early in life [29] (figure 2). As a consequence, the output of mature naive T cells from the thymus decreases with age, leading to severely reduced numbers of naive T cells in the periphery in elderly persons [30, 31]. Naive T cells are generally characterized by surface markers, such as CD28, CD27, CD45RA, and CCR7; by long telomeres, which indicate a short replicative history; and by a highly diverse T cell receptor repertoire. In addition to there being a reduced number of phenotypically naive (CD45RA−CD28+) T cells, the remaining CD45RA−CD28− T cells are functionally deficient in elderly persons. They have shortened telomeres and a restricted T cell receptor repertoire, suggesting past homeostatic proliferation leading to the expansion of T cells with certain specificities and to the loss of others [32]. This numerical and functional impairment of naive T cells hampers the induction of adaptive immune responses to neoantigens. In the context of primary vaccination, this leads to reduced response rates. Naive antigen-inexperienced T cells are also functionally deficient and difficult to prime in aged mice [33].

Memory T cells are crucial in controlling humoral and cellular immune responses. For sustained protective immunity, it is therefore necessary to induce a functional T cell memory following immunization. Experiments in mice have shown that memory T cells generated from aged naive T cells survive and persist well in vivo but are markedly defective in their proliferation and cytokine secretion during recall responses. In contrast, memory cells generated in young animals retain their function for extended periods of time [34]. Similar to aged mice, healthy elderly persons are able to mount a T cell response after vaccination but exhibit an impaired long-term immune response [34]. These findings emphasize the importance of early primary immunization to guarantee intact immunologic memory in old age.

The decrease in naive T cell counts in elderly persons is accompanied by the accumulation of highly differentiated effector T cells. Characteristics of highly differentiated effector T cells are short telomeres, a highly restricted T cell receptor repertoire, an impaired capacity to migrate to lymph nodes, and a decreased ability to be stimulated by antigen-presenting cells, a result of the loss of the costimulatory molecules CD28 and CD27 [35]. CD28− effector T cells also produce high amounts of the proinflammatory cytokine IFN-γ, which contributes to the high inflammatory background typical of old age [36], supporting the development and progression of age-related diseases, such as osteoporosis, atherosclerosis, and neurodegeneration [37]. The accumulation of CD28− effector T cells has also been shown to be correlated with impaired humoral responses to influenza vaccination [38, 39]. However, CD28− effector T cells are a heterogeneous cell population, particularly during old age, and some studies suggest that a subpopulation of these cells has functional defects (e.g., increased expression of PD1) [40]. Of note, chronic infections substantially contribute to the replicative exhaustion of the peripheral T cell pool. Lifelong infection with cytomegalovirus is associated with increased numbers of cytomegalovirus-specific CD28− effector T cells in young and elderly persons [41]. These cells occur as expanded clones and dominate the peripheral T cell pool, hampering the propagation of other T cell specificities (e.g., Epstein-Barr virus–specific T cells) [42] and thus endangering diversity [43], homeostasis, and successful immunization within the aged immune system.

B cells also undergo age-related changes that further aggravate functional defects of the adaptive immune response. Similar to the T cell system, naive B cell numbers decrease and effector B cells accumulate in old age. This leads to a reduction in the diversity of antibody responses [44]. Defects in isotype switching and somatic mutation, both of which are essential for the production of high-affinity IgG antibodies, result in weak and low-affinity antibody responses in elderly persons [45]. The number of long-lived plasma cells in the bone marrow is reduced in old mice, probably because of an impaired ability of the aged bone marrow to support survival of plasma cells [46]. Additionally, interactions of aged B cells with T helper cells are disturbed in elderly persons, because senescent CD4+ T helper cells have a reduced expression of CD154 (CD40L) [47], a molecule of crucial importance for the stimulation of B cells by T cells.

Because antibody titers are declining faster in elderly persons [11] and because the success of booster vaccination clearly correlates with prebooster antibody titers [9], optimization of immunization schedules seems advisable. Regular vaccination during young adulthood may be a prerequisite for successful booster vaccination in old age.

Little information is yet available on the effect of live atten-
uated vaccines on the aged immune system. Childhood vaccination with these vaccines should, by definition, induce long-lasting antibody production and strong cytotoxic T lymphocyte responses. However, because routine vaccinations of children against measles, mumps, and rubella have been performed for <40 years, there are no data available regarding whether childhood immunization with live attenuated vaccines is still protective in old age. A recent publication reports that the number of CD4+ T cells specific for measles virus decreases with age in vaccinated persons [48]. It will be important to determine whether booster immunizations would be advisable for persons vaccinated with live attenuated vaccines during childhood. Primary immunization with live attenuated vaccines in old age may be associated with an increased risk of adverse effects. Thus, it has been suggested that advanced age is a risk factor for severe systemic adverse effects associated with the application of yellow fever vaccine [18]. This may be due to low numbers and functional defects of naive T cells, indicating that an aged organism may not be capable of coping with a new pathogen, even in the case of attenuated vaccine strains. To avoid adverse effects in elderly persons, safer live attenuated vaccines are needed. The first generation of live attenuated vaccines was produced by serial passages in cell culture, which leads to an unspecific loss of pathogenicity. Development of new live attenuated vaccines includes rationally designed attenuation, for example, by the deletion of individual genes. These new vaccines should be specifically tested for use in elderly persons and should provide an improved safety profile. An alternative strategy for successful immunization with live attenuated vaccines might be to apply live attenuated vaccines only earlier in life, followed by booster vaccination with inactivated or adjuvanted subunit vaccines in old age.

CONCLUSIONS

The frequency and severity of infectious diseases increase with old age. Infections carry a substantial risk of illness, loss of independence, disability, and death in elderly persons. They, thereby, contribute to the socioeconomic burden associated with rising life expectancy. Vaccinations provide efficient protection from infectious diseases. Age-related changes in the immune system may hamper successful vaccination. Vaccines tailored to the needs of the aging immune system will have to be developed, and vaccination schedules will have to be adapted to improve protection in elderly persons. A better insight into the basic mechanisms of immune dysfunctions that occur with age will help to fulfill this task, in order to ensure protection of the vulnerable elderly population.

Acknowledgments

Financial support. Austrian Science Fund (project S9308-B05) and the European Union (Network of Excellence “LifeSpan” [FP6 036894]).

Potential conflicts of interest. All authors: no conflicts.

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