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Vaccination indications and limits in the elderly

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Abstract

Infections are a major cause of morbidity and mortality in the elderly. Although vaccination is crucial for preventing infectious diseases, the ability of the elderly to establish an effective immune response to vaccination is much lower compared to the younger population. In most industrialized countries, four vaccines are now recommended for people over 60 years of age: influenza vaccine, pneumococcal vaccine, herpes zoster vaccine, and a vaccine combining tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis. Only the last vaccine provides an adequate antibody response. The influenza and pneumococcal vaccines seem to be able to alleviate disease. The herpes zoster vaccine somewhat prevents reactivation of herpes zoster and decreases the severity of postherpetic neuralgia. Recent technological advances and novel adjuvants are providing new opportunities for improving vaccination of the elderly. Lifelong vaccination schedules should be promoted in order to achieve the herd immunity threshold. Maintaining the health of the population requires moving from a childhood-based vaccination strategy to a more balanced vaccination program throughout life.

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Introduction

Infections are a major cause of morbidity and mortality in the elderly. The diagnosis of infectious diseases is more challenging in the elderly due to subtle and non-specific clinical signs and symptoms as well as treatment, which is often complicated by multidrug resistance (1, 2). Therefore, prevention of infections in the elderly is crucial, especially in terms of vaccination.

The crucial problem connected with vaccination in the elderly is their lower ability to mount an effective immune response to vaccination than in the younger population (1-5). Namely, both innate and adaptive immune system functions are affected by aging. This process is termed immunosenescence. Immunosenescence is the main reason for lower immunogenicity and effectiveness of vaccines in the elderly (2, 5, 6). Impaired ability to respond to new antigens and unsustained memory responses are two of the cardinal features of immunosenescence that influence vaccination effectiveness (2). Other important features include impaired antigen uptake and presentation of antigen by antigen-presenting cells, lower numbers of naive T cells due to thymic involution and a lower diversity of the T cell repertoire, lower numbers of naive B cells, impaired isotype switching, and somatic hypermutation, which leads to weaker antibody responses with lower affinity (6). A summary of functions affected by aging is provided in Table 1 (5).

Another important issue is that most vaccines currently on the market were developed in a society in which the average life expectancy was 60 to 65 years (1). Today's society in most regions of the world has a much higher proportion of the elderly, and life expectancy is further increasing.

This review briefly summarizes the most recent relevant data regarding vaccination in the elderly. It encompasses current guidelines, controversies, challenges, and opinions. In most countries, four vaccines are now recommended for people over 60: influenza vaccine, pneumococcal vaccine, herpes zoster vaccine, and a vaccine combining tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) (2). A comparison of vaccination recommendations in three selected European countries (including Slovenia) and the United States is presented in Table 2 (3-5).

Table 1 | A summary of main changes in the immune system due to immunosenescence.

Affected cells	Function affected by aging
NK cells	Elimination of infected cells/cytotoxicity
	Production of cytokines
Neutrophil and monocyte/ macrophage	Chemotaxis
	Elimination of pathogen/microbicidal function
	Phagocytosis
	TLR-signaling
Dendritic cells	Phagocytosis
	Antigen presentation
T-cells	↓ naive T cells (CD4 and CD8)
	↑ antigen-experienced T cells (CD4 and CD8)
	↓ T cell diversity
CD4 T-cells and B-cells	High-affinity antibody responses
B-cells	↓ naive B cells
	Class-switch recombination, somatic hypermutation
	Reduced repertoire (↓ response to neo-antigens)

Pneumococcal vaccine

The clinical spectrum of pneumococcal infections ranges from sinusitis and acute otitis media to meningitis and pneumonia (7). *Streptococcus pneumoniae* is the leading cause of community-acquired pneumonia.

The elderly are at substantially increased risk for pneumococcal infections. A major goal of pneumococcal vaccination in the elderly is prevention of hospitalization and death, especially due to invasive pneumococcal disease (IPD)–the condition defined by microbiological detection (mainly isolation) of *S. pneumoniae* from a normally sterile site.

The currently available vaccine is a 23-valent pneumococcal polysaccharide vaccine (PPV23), which is also recommended for the elderly in several countries. However, being a polysaccharide vaccine, it induces only T cell–independent antibody responses and does not induce immunological memory (5). In a recent Cochrane meta-analysis on vaccines for preventing pneumococcal

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infections in adults, the authors provided strong evidence supporting the recommendation for PPV to prevent IPD in adults (OR 0.26, 95% CI 0.14 to 0.45). However, there was not enough evidence to support the routine use of PPV23 to prevent all-cause pneumonia or mortality (OR 0.90, 95% CI 0.74 to 1.09) (8). The inclusion criteria were met for 25 studies: 18 randomized control trials (RCT) involving 64,852 participants and seven non-RCTs involving 62,294 participants.

A recently developed pneumococcal protein-conjugated vaccine (PCV) is more immunogenic than PPV23 and it induces a T cell–dependent immune response. Although it is also more effective in the elderly, it is mostly used for prevention of IPD and otitis media in infants and young children. An initially used heptavalent PCV (PCV7) has mostly been replaced recently with a conjugated vaccine containing 13 different serotypes (PCV13) (5). PCV13 was approved by the U.S. Food and Drug Administration (FDA) in December 2011 for use in people 50 and older. Recently, it was also approved for extended use in the European Union for adults 18 to 49 years old and is now also approved in more than 80 countries for use in adults 50 and older (9).

In a recent randomized, modified double-blind trial of 936 adults 70 and older that had previously received PPSV23 at least 5 years before study entry and were now vaccinated with PCV13 or PPSV23, PCV13 was significantly more immunogenic than PPSV23 (10). The same group also published a study in which 60- to 64-year-olds that were initially given PCV13 received PCV13 or PPSV23, and those initially given PPSV23 received another PPSV23 (11). The authors concluded that initial vaccination with PCV13 establishes an immune state that results in recall upon subsequent vaccination. However, after initial vaccination with PPSV23, subsequent PPSV23 vaccination induces lower responses compared with the initial vaccine (11).

Using a Markov model, Smith et al. recently determined the cost-effectiveness of PCV13 and PPV23 in older U.S. adults (65 or 75 years). PPV23 vaccine was more expensive and less effective than conjugate PCV13 vaccine. Therefore, single-dose PCV13 strategies may be economically reasonable for the elderly (12).

Regular annual influenza vaccination provides an opportunity to concomitantly administer both influenza and pneumococcal vaccines. Previous studies have shown that PPV23 and trivalent influenza vaccine can be safely co-administered (13). More recently, a randomized double-blind trial evaluated the immunogenicity and safety of PCV13 given concomitantly with trivalent influenza vaccine in the elderly. The authors confirmed acceptable immunogenicity and safety compared with either vaccine given alone (14).

Unfortunately, pneumococcal vaccine coverage is still very low in most European countries. In 2011, pneumococcal vaccine coverage in the U.S. was 62.3% (a 2.6% increase from 2010) (15), but in France only 10% of hospitalized patients over 75 received the vaccine (16). A recent study investigated some potential aspects of low vaccine coverage in terms of awareness of pneumococcal infection among primary care physicians and specialists from 13 western European countries (17). They found relatively low awareness of the term IPD: only 50% of physicians in primary care and 71% of specialists were able to provide a correct definition of IPD. The survey also highlighted the importance of physician recommendations for vaccination in encouraging patients to be vaccinated (17).

In conclusion, although current recommendations for vaccinating the elderly against pneumococcal infections in many countries include PPV23 only, due to recent data on immunogenicity and the effectiveness of novel pneumococcal vaccines, future recommendations will most probably also include PCV13.

Influenza vaccine

Seasonal influenza is a public health challenge with several important economic and social implications. The best available method for prevention of influenza is vaccination. Annual vaccination against influenza is generally recommended for elderly individuals, although with different age limits in different countries (Table 2).

The effectiveness of inactivated trivalent influenza vaccine is variable in different age groups. In general, any type of influenza vaccine is less effective among the elderly than in the young population. In randomized placebo-controlled clinical trials of healthy adults, the influenza vaccine was 70 to 90% effective (8), but projected clinical efficacy in the elderly is 17 to 53% for all three antigens (18, 19). Some progress in clinical efficacy is being made with new licensed adjuvants, such as MF59 and AS03, use of higher antigen dosage, shortened booster intervals, and increased number of doses. Alternative routes of application such as intradermal or intranasal are also being explored.

The most recent Cochrane meta-analysis on vaccines for preventing influenza showed that influenza vaccines have a modest effect on reducing influenza symptoms and working days lost in adults (20). Meta-analysis found no evidence of effect on influenza-associated complications, such as pneumonia, or transmission rates. Due to the poor quality of the evidence, the authors did not draw any conclusions regarding the effects of influenza vaccines for people 65 or older (20).

In a recent study using the instrumental variable analysis method, the authors investigated the impact of influenza vaccination on all-cause mortality and tried to establish an unbiased estimate of influenza vaccine effectiveness (21). Individuals over 65 were followed for nine influenza seasons (2000/2001–2008/2009), which amounts to more than 12 million person–influenza seasons of observation. The study showed that influenza vaccination is not associated with reduction in mortality alone, but there may be an association with reductions in the composite of pneumonia and influenza hospitalizations and all-cause mortality (21).

Table 2 | Comparison of vaccination recommendations for the elderly in four countries in 2011.

	Slovenia	Austria	Germany	U.S.
S. pneumoniae (polysaccharide)	Once over 65	Once over 65	Once over 60	Once over 65 *(repeated vaccination recommended for risk groups)*
Influenza	Annual over 65	Annual over 50	Annual over 60	Annual
Diphtheria	Every 10 years	Over 60 every 3 years	Every 10 years	Every 10 years
Tetanus	Every 10 years	Over 60 every 3 years	Every 10 years	Every 10 years
Pertussis	Not recommended	Over 60 every 3 years	Once during adulthood	Once during adulthood
Varicella-Zoster	Not recommended	Once over 50	Not recommended	Once over 60
Tick-borne encephalitis	Over 60 every 3 years	Over 60 every 3 years	In risk areas only	Not recommended

Recently, the MF59-adjuvanted trivalent inactivated vaccine was developed to increase the immune response of the elderly to influenza vaccination. It is considered more immunogenic than the conventional non-adjuvanted vaccine (22). A study carried out in northern Italy sought to establish its effectiveness in individuals at least 65 years old. The risk of hospitalization for influenza or pneumonia was 25% lower for the MF59-adjuvanted vaccine relative to trivalent inactivated vaccine (relative risk = 0.75, 95% CI 0.57 to 0.98) (23).

The largest randomized trial of influenza vaccine in the elderly was recently performed in 15 countries worldwide during two influenza seasons (2008–09 and 2009–10) (24). AS03-adjuvanted inactivated trivalent influenza vaccine (TIV) was compared to non-adjuvanted TIV for seasonal influenza. The authors reported that an AS03-adjuvanted inactivated TIV has a 12% higher efficacy than the non-adjuvanted vaccine, but this difference was not significant (274 [1.27%, 95% CI 1.12–1.43] of 21,573 vs. 310 [1.44%, 1.29–1.61] of 21,482; relative efficacy 12.11%, 95% CI –3.40 to 25.29). They also suggested that the benefit of influenza vaccination in the elderly might vary depending on influenza subtypes. The greatest efficacy was against influenza A H3N2 (170 [0.79, 0.67–0.92] vs. 205 [0.95, 0.83–1.09]; post-hoc analysis relative efficacy 22.0%, 95% CI 5.68–35.49). The authors concluded that there is a benefit of use of adjuvanted vaccine for preventing death and pneumonia (24).

The average EU vaccination rate for influenza in 2010 was 45.3% for the population 65 and over. The Netherlands had the highest coverage, at 77%, whereas the lowest documented coverage was in Estonia (1%). The vaccination rate in Slovenia in 2010 was low, only 18% (25). At the EU level there was a considerable increase in vaccination rates for influenza in the elderly from 2000 to 2005 (from 45% to 54% on average), followed by a decline in vaccination in 2010. However, in Slovenia the influenza vaccination rate was similar in 2000 and 2005 (35%), followed by a decline to the 18% mentioned above in 2010 (26).

Seasonal influenza vaccine uptake in the elderly is influenced by many social determinants: structural, intermediate, and healthcare-related. Factors related to the healthcare system comprise another group of determinants of vaccination uptake. These factors include the quality, credibility, and persuasiveness of physicians' advice, accessibility, affordability, knowledge, and general attitudes toward vaccination (27). An important additional strategy of optimizing influenza vaccination in the elderly is indirect protection of the elderly through vaccination of other population groups that could come in close contact with elderly individuals. This first includes vaccination of children, who most efficiently transmit the virus, and, second, vaccination of healthcare workers, particularly in long-term care facilities.

Herpes zoster vaccine

Primary infection with the varicella zoster virus (VZV) causes chickenpox, which usually occurs in children. After the illness has resolved, the virus remains latent for life in the dorsal spinal ganglia and can be reactivated as a neurocutaneous disease, herpes zoster, when immunity to VZV declines. This painful and long-lasting condition can often significantly impair the patient's quality of life and is especially detrimental for the elderly. The reduction of cellular immunity due to immunosenescence predisposes the elderly to VZV reactivation, and therefore the incidence of herpes zoster increases with age (28). Complications such as postherpetic neuralgia, characterized by persistent pain for prolonged periods of time, occur in almost 50% of older persons (29).

Vaccination with an attenuated live form of VZV acts by boosting declining preexisting specific cellular immunity, therefore avoiding VZV reactivation (30). Current herpes zoster and VZV vaccines both contain the same attenuated VZV Oka strain but the zoster vaccine has at least 14-times higher potency (29, 31). The zoster vaccine (Zostavax; Merck) was licensed by the FDA in 2005 and is recommended for routine use in immunocompetent adults over 60 (30). Currently it is contraindicated for use in immunocompromised patients.

In 2005, Oxman et al. (29) determined incidence rates of postherpetic neuralgia and herpes zoster among vaccinated and non-vaccinated older adults in a randomized, double-blind, placebo-controlled trial. Incidence rates were significantly lower among the vaccinated than in the placebo group and the researchers concluded that vaccination of immunocompetent elderly persons with the Oka strain–based vaccine decreases both morbidity associated with herpes zoster and the incidence of postherpetic neuralgia (29).

Recently, a large "real-life" cohort study on herpes zoster vaccine effectiveness and influence of vaccination on the incidence of postherpetic neuralgia was published (32). More than 750,000 eligible individuals over 65 from the U.S. were enrolled. Even though the vaccine uptake was low (3.9%), herpes zoster vaccination was associated with a significant reduction in the incidence of zoster, even among immunosuppressed individuals. Adjusted vaccine effectiveness against incident zoster was 0.48 (95% CI 0.39–0.56) and 0.37 (95% CI 0.06–0.58) for the total cohort and for immunosuppressed individuals, respectively. Vaccine was also associated with a lower incidence of postherpetic neuralgia: effectiveness against postherpetic neuralgia was 0.59 (95% CI 0.21–0.79) (32).

In a Cochrane review of vaccines for preventing herpes zoster in adults published in 2012, eight randomized controlled trials with a total of 52,269 participants were included (31). Three studies were classified at low risk of bias. The review suggests a clear benefit in vaccinating the elderly with the herpes zoster vaccine. The vaccine is safe and well tolerated. Patients that received the vaccine had fewer confirmed cases of herpes zoster than those that received a placebo (risk ratio 0.49 (95% CI 0.43–0.56)). The benefit was greatest in participants 60 to 69 years old, although this age group was associated with more adverse events (31).

In another recent study, Morrison et al. confirmed the general safety of zoster vaccine in elderly patients with a recent history of herpes zoster (33). Serious adverse events occurred in 1.37% of all vaccinated individuals, but there were no significant differences between those with or without a prior history of herpes zoster. Their results demonstrate that the vaccine is generally safe and also well tolerated in this population. Furthermore, their results further support the U.S. Centers for Disease Control and Prevention (CDC) recommendations to administer herpes zoster vaccine to all individuals above 60 regardless of a history of recent herpes zoster (33).

Special consideration should be given to elderly patients with depression because they have diminished cell-mediated immunity responses to herpes zoster vaccine (34). If depression is left untreated, there is a higher likelihood of failure to respond to vaccination due to reduced baseline levels of VZV-specific responder cells. The risk and severity of herpes zoster thus may be increased. If patients are treated, immune responses to vaccination are normalized (34).

Td and Tdap vaccines

In many countries, tetanus and diphtheria booster doses are recommended every 10 years throughout the entire lifetime (Table 2). Booster vaccination against tetanus and diphtheria is most practically performed using combined tetanus-diphtheria vaccine or Td vaccine. Regular Td booster vaccinations throughout adulthood not only ensure sustained protection against tetanus and diphtheria, but are also crucial for successful vaccination in older age because the effectiveness of every booster vaccination depends mainly on the concentration of B memory cells and residual antibodies (5).

The tetanus toxoid, reduced diphtheria toxoid, acellular pertussis vaccine (or Tdap vaccine) is a newly designed combined vaccine against three infectious diseases: tetanus, diphtheria, and pertussis. Pertussis vaccination is currently only recommended as a single dose of Tdap across all adult age groups. It can be administered regardless of the interval since the last Td vaccine (35). In July 2011, the U.S. FDA approved expanding the age indication for Tdap to 65 or older, and a year later the U.S. Advisory Committee on Immunization Practices recommended Tdap for all adults 65 and older (35). Unfortunately, not many countries in the world (including EU countries) follow the U.S. recommendation for pertussis vaccination in the elderly, although it is well known that the incidence of pertussis in the elderly is increasing (36) and that pertussis in adults is greatly underdiagnosed and underreported (37). In our opinion, it is therefore crucial that the EU reconsider current pertussis vaccination strategies for the elderly and follow the U.S. path as soon as possible.

The safety and immunogenicity of the Tdap vaccine in adults 65 and older has been established in many studies (38, 39). A more recent study by Tseng et al. evaluated the safety of Tdap vaccine when used off-label in the elderly (40). They compared prespecified adverse events in the elderly that received either the Tdap or Td vaccine in more than 119,000 vaccinees in each group. They found a slightly increased risk of inflammatory/allergic events up to 6 days following both Tdap and Td, but the risk of adverse events was comparable for both vaccines (40).

Other vaccines

An increasing number of travelers are of advanced age. There are many vaccine-preventable diseases affecting travelers, such as typhoid, yellow fever, Japanese encephalitis, hepatitis A, hepatitis B, rabies, and so on. Vaccination will be the first contact with a new antigen for most senior travelers, and so they will probably not fully respond to this antigen because the naive cell repertoire decreases with age. Furthermore, most available immunization guidelines for travel vaccines are obtained from studies including young (male) adult participants only, and so it is questionable whether derived efficacy data can also automatically be considered for the elderly population (5). Nevertheless, elderly travelers should be offered a full spectrum of vaccines against vaccine-preventable diseases before travel, but for the reasons described above in a more advance phase than for younger travelers.

Among Europe-specific vaccine-preventable diseases, tick-borne encephalitis should be considered with special care. Vaccination against tick-borne encephalitis with an inactivated vaccine is recommended in 27 European countries, including Slovenia, without age restrictions (5). Booster immunizations should be given at 3-year intervals for those 50 or older (41).

Conclusions

Vaccine-preventable diseases still cause severe morbidity and mortality among the elderly. Vaccination of the elderly remains the best strategy to prevent infection, but is suboptimal because of immunosenescence. Thus, lifelong vaccination programs should be promoted in order to achieve the herd immunity threshold, moving from the current concept of childhood-based vaccination to more balanced lifelong vaccination schedules (42).

Table 3 | Currently recommended vaccines in the elderly and future prospects.

	Limits	Benefits	Prospects
Pneumococcal vaccine	PPV23 does not induce immunological memory.	PCV13 is safe, more immunogenic, and economically reasonable.	A vaccine covering all pneumococcal serotypes.
Influenza vaccine	Variable effectiveness, substantially lower in the elderly.	More immunogenic with new adjuvants, such as MF59 and AS03.	A universal pan-influenza vaccine. Live recombinant viral vectors for the delivery of influenza antigens, proteosome vaccines and DNA-based vaccines. Cutaneous or intradermal administration.
Herpes zoster vaccine	Contraindicated in immunocompromised, less effective in elderly patients with untreated depression.	Effective, generally safe, and well tolerated.	Inactivated herpes zoster vaccine for immunocompromised patients.
Tdap vaccine		A safe and immunogenic vaccine. Can be co-administered with influenza vaccine.	Reconsidering recommendations and current vaccination strategies for pertussis.
Other vaccines			Vaccines for hospital-acquired bacterial infections.
All vaccines for the elderly			Higher dose of antigen, shorter booster intervals. Intradermal or intranasal administration. Novel adjuvants (mineral salts, oil-in-water emulsions, TLR agonists, liposomes, and combination adjuvants). Enhancing immunity in the elderly (restoring the generation of B and T cell precursors, rejuvenating thymic function).

An overview of currently recommended vaccines for the elderly and future prospects is presented in Table 3 (1, 41-43). Briefly, all four vaccines described in detail above boost preexisting immunological memory. Only the Tdap vaccine gives a satisfactory antibody response in the elderly compared to the response in young adults (39). Influenza and pneumococcal vaccine seem to be able to alleviate disease but do not induce protective immunity in a large proportion of the elderly. Herpes zoster vaccination somewhat prevents reactivation of herpes zoster and decreases the severity of postherpetic neuralgia (2).

In recent years, research in this field has mainly focused on improving existing adjuvants and designing novel ones that enhance or modulate vaccine-induced immune responses. These include combinations of novel TLR agonists, liposomes, saponins, glycolipid a-galactosylceramide, and so on, which might also improve the immunogenicity of various antigens in the elderly (1, 43). How the immune system ages and which molecular pathways can be targeted to improve responses to vaccination in the elderly are two issues we are only beginning to understand. Due to the rapid development of new technologies, we may soon be able to develop vaccines against new pathogens and, more importantly, improve the safety and efficacy of existing vaccines. Developing a universal pan-influenza vaccine, a universal pneumococcal vaccine covering all serotypes, or an inactivated herpes zoster vaccine for immunocompromised patients are some of the achievable goals in the coming years.

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