CHAPTER 10

The Efficacy of Vaccines to Prevent Infectious Diseases in the Elderly

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Abstract

Infectious diseases still represent a major challenge to human progress and survival. Especially elderly persons are more frequently and severely affected by infectious diseases and they display distinct features with respect to clinical presentation and treatment. Although vaccinations are considered a vital medical procedure for preventing morbidity and mortality caused by infectious diseases, the protective effect of vaccinations is abrogated in elderly persons. This is due to a decline in the functions of the immune system referred to as immunosenescence. The first part of this chapter will therefore summarize the status quo of the efficacy of vaccines in preventing morbidity and mortality caused by typical infectious diseases in the elderly, such as influenza, pneumonia and tuberculosis. The second part will then elucidate the underlying age-related mechanisms which may contribute to the decreased efficacy of vaccines. Based on the complex mechanisms involved in immunosenescence, strategies will be outlined which may be successful in enhancing protective immune responses following vaccination in elderly persons.

Introduction

With respect to the current demographic development in many countries, including the European Union and the United States of America, infectious diseases in geriatric patients are becoming an increasingly important issue. Infections in elderly persons are not only more frequent and more severe, but they also have distinct features regarding clinical presentation, microbial epidemiology and treatment. Urinary tract infections, lower respiratory tract infections, skin and soft tissue infections, infective endocarditis, bacterial meningitis, tuberculosis and herpes zoster appear to have a higher prevalence in elderly persons. In developed countries like the United States, pneumonia, influenza and septicemia are ranked among the ten major causes of deaths in people aged 65 years and older.[1] The reasons for the increased susceptibility to infectious diseases include epidemiological elements, immunosenescence, malnutrition and age-dependent anatomical alterations.

Infectious diseases still represent a major challenge to human progress and survival as they are responsible for about 20% of all deaths in the world. This is not only related to microbial and viral factors but also to social and environmental determinants, such as social upheaval, urbanization, air travel, natural disasters and climate change.[2] Newly emerging infectious diseases include acquired immune deficiency syndrome (AIDS), hepatitis C, several hemorrhagic fevers, severe acute respiratory syndrome (SARS) and avian influenza. The resurgence of several other infectious diseases is supported by the increased occurrence of multiple drug-resistant microorganisms such as *Staphylococcus aureus*, *Mycobacterium tuberculosis*, *Escherichia coli* and *Streptococcus pneumoniae*.

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Altogether, this represents an enormous economic burden on health care systems all over the world. For instance, the annual costs of medical care for treating infectious diseases in the United States alone is about $120 billion and for treating antimicrobial-resistant infections it may be as high as $5 billion.[3]

A great success story was the implementation of large-scale vaccination strategies that led to the eradication of smallpox in 1980[4] and to a drastic reduction of poliomyelitis, tetanus, diphtheria, measles, pertussis and meningitis. Presently, vaccinations are still considered the most cost-effective medical procedure for preventing morbidity and mortality caused by infectious diseases. 26 different infectious diseases can be prevented by vaccinations and 61 vaccines are being developed according to a 2004 survey by the Pharmaceutical Research and Manufacturers of America.[5] The new candidate vaccines are intended to provide protection against diseases caused by rotavirus, herpes zoster and papilloma virus and will be available from 2007 onwards (Table 1). But also improved vaccines against influenza, pneumonia and tuberculosis are currently being tested in clinical trials (Table 1). This chapter now outlines the relevance of vaccines to fight infectious diseases in old age and how age-related changes within the immune system contribute to the decreased efficacy of vaccines. It also discusses the progress made in the development of vaccines with improved immunogenicity in elderly persons.

The Role of Vaccines in Fighting Infectious Diseases in Old Age

Outbreaks of deadly infectious diseases such as Ebola, Marburg, SARS or the H5N1 avian influenza regularly alert the world, whereas there is not much public attention paid to infectious diseases that cause substantial morbidity and mortality among the elderly population. For instance, influenza, invasive *Streptococcus pneumoniae* infection, urinary tract and skin infections have a higher prevalence in elderly persons.[6] Old individuals may also fail to respond sufficiently to therapy and frequently suffer from opportunistic infections, recurrent infections with the same pathogen or reactivation of latent diseases, such as those caused by *Mycobacterium tuberculosis* or the Varicella zoster virus. There are no vaccines available for many infectious pathogens that are frequent in elderly subjects and existing vaccines are underused and often do not assure such an effective protection as in young subjects. The following paragraphs will highlight the most important infectious diseases which threaten the elderly population and will provide information on epidemiology, vaccine availability and efficacy, vaccination coverage and general health authority recommendations.

Influenza

Influenza is a highly contagious, acute viral respiratory disease that causes significant morbidity and mortality. The annual outbreaks affect approximately 5-20% of the population worldwide with 3-5 million cases of severe illness and up to one million deaths each year. Especially elderly people and persons that are chronically ill or otherwise immunocompromised are at enhanced risk. For example, during influenza epidemics, Barker and Mullooly reported two deaths per 100,000 healthy people below 65 years of age compared with 797 per 100,000 in those over 65 with two or more high-risk conditions.[7] In contrast to measles, smallpox and poliomyelitis, influenza is caused by viruses that undergo continuous antigenic variation and possess an animal reservoir. Therefore, we are recognizing annual epidemics that have been interrupted by three pandemics (Spanish influenza, H1N1, 1918-1919; Asian influenza, H2N2, 1957-1958 and Hong Kong influenza, H3N2, 1968), caused by new influenza virus strains with increased virulence.

Influenza viruses are enveloped viruses containing eight single-stranded RNA segments which encode for viral proteins, such as hemagglutinin (HA), neuraminidase (NA), matrix protein (M1) and nucleoprotein (NP) (Fig. 1). Influenza viruses belong to the family Orthomyxoviridae and are divided into three genera, influenza virus A, B and C, based on antigenic differences in two of their structural proteins, M and NP. Disease symptoms caused by Influenza C are rare whereas Influenza B often causes sporadic outbreaks, especially in residential communities like nursing homes. Influenza A viruses are further divided into subtypes according to the antigenicity of their

Table 1. The developmental status of vaccines against some human pathogens

Disease or Pathogen	Product Name	Company	Type of Vaccine	Developmental Status
Cytomegalovirus	-	Chiron	subunit	phase II
	-	Sanofi Pasteur	live-attenuated	phase II
	-	Vical	nucleic acid	phase I
Herpes zoster (Shingles)	Zostavax	Merck and Co	live-attenuated	preregistration
	-	GSK	subunit	phase I
Human papillomavirus	Cervarix	GSK, MedImmune	virus-like particle L1 + adjuvant AS04	preregistration
	Gardasil	Merck and Co	virus-like particle L1	preregistration
Influenza	CAIV-T	MedImmune, Wyeth	live-attenuated	licensed in the US
	FluMist	MedImmune	nasal, live-attenuated	phase III
	-	Chiron	cell-culture based	phase III (Europe)
	FluBLOK	Protein Sciences	subunit, cell-culture based	phase III
	FluINsure	ID Biomedical	nasal, subunit	phase III
	Fluviral	ID Biomedical	split-virus	phase III
	-	GSK	subunit	phase I, II
	-	Protein Sciences	subunit (H5)	phase I
Pneumonia	-	Wyeth	9-valent conjugate	phase III
	Streptorix	GSK	11-valent conjugate	phase III
	StreptAvax	ID Biomedical	subunit	phase II
	-	GSK	subunit	phase I
Rotavirus	Rotateq	Merck and Co	live-attenuated	preregistration
	Rotarix	GSK, Avant Ther.	oral, live-attenuated	preregistration
Tuberculosis	rBCG30	Aeras Global TB Vaccine Foundation	live-attenuated	phase I
	-	GSK	subunit + adjuvant AS02A	phase I
	-	Corixa	subunit	phase I
Varicella, Mumps,		GSK	live-attenuated	phase III
Measles, Rubella		Merck and Co	live-attenuated	phase III

GSK, GlaxoSmithKline; adapted from ref. 88.

major envelope glycoproteins, HA and NA. With at least 15 different hemagglutinin and 9 different neuraminidase subtypes, there is considerable antigenic variation among influenza viruses. The human influenza viruses are currently limited to three hemagglutinin (H1, H2 and H3) and two neuraminidase subtypes (N1 and N2), whereas birds are the predominant hosts for the other subtype strains. HA initiates viral infection by binding to sialic acid residues on the carbohydrates of glycoproteins present on epithelial cells of the respiratory tract. Therefore, high-affinity IgA and IgG antibodies against HA may prevent infection from influenza virus. In contrast, NA cleaves the sialic acid from viral and cellular proteins to promote the release of newly synthesized influenza viruses from the infected host's plasma membrane.

Although antiviral drugs with moderate efficacy are available, active immunization represents the most vital element in the prophylaxis of influenza disease. However, the frequently occurring
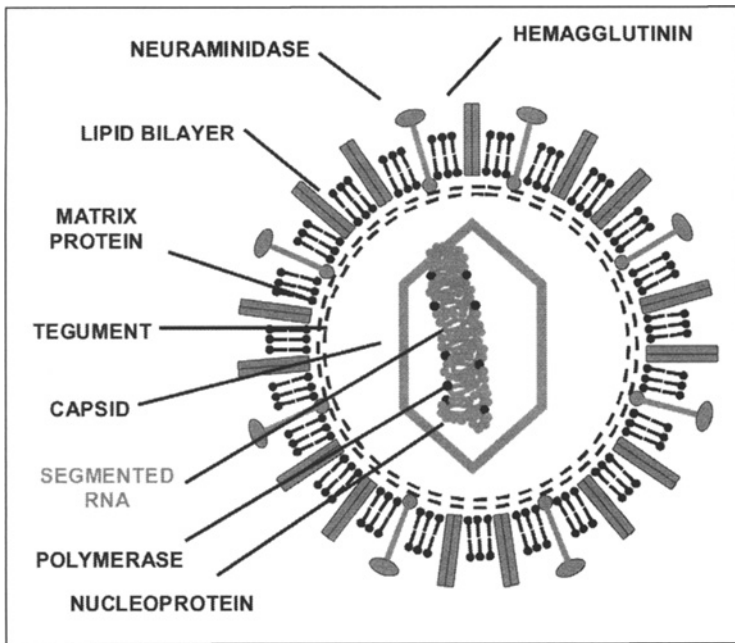
Figure 1. Schematic representation of the influenza virus structure. See text for more details.

antigenic drift requires an annual modification of the vaccine components according to the recommendations of the WHO. Therefore, vaccination has to be repeated annually to ensure protection against the circulating influenza strains. But vaccination coverage differs largely within European countries. In 2002, the rate of vaccine distribution was highest in Spain, Belgium, The Netherlands, United Kingdom and Germany (between 18.1 and 20.3%) and lowest in Poland, Czech Republic, Lithuania and Latvia (between 1.9 and 7.1%). Canada and the United States had the highest rate of vaccine distribution, being 32.8 and 28.9%, respectively. Remarkably, 70% of US citizens aged 65 and above have been vaccinated against influenza.[8] Although there are several vaccines available, the efficacy of many vaccines in preventing influenza disease in elderly persons is only around 56%.[9] Especially very old and frail persons show a decreased response to influenza vaccines.[10] The reduced vaccine efficacy is due to low levels of IgA and IgG antibodies, delayed peak antibody titers and shortened maintenance of titers after vaccination. Nevertheless, immunization in elderly people has been shown to be safe, cost-effective and associated with reduced rates of hospitalization and influenza-related deaths.[11,12] In particular, the efficacy of influenza vaccination to reduce mortality in elderly people is greater after repeated annual vaccination than after first administration.[13] Presently, influenza vaccines can be classified in split-virus, subunit, virosomal and live-attenuated vaccines (Table 2). Split-virus vaccines are used since the 1980s, are cheap and offer a good protection for children above 6 months of age and adults. Recently, subunit vaccines with new adjuvants have been developed (Fluad®, Addigrip®) that show an increased immunogenicity, a favorable safety profile and may be more suitable for the vaccination of elderly persons.[14] Additionally, invariant antigens, such as M1 and NP, may also play an important role in protection and could be used in vaccines to induce long-lasting immunity to a variety of different influenza strains. Another strategy to enhance immunogenicity may the use of virosomes that are nontoxic, biodegradable lipid-based antigen-presentation systems.[15] Virosomal influenza vaccines, such as Inflexal V®, Influvac Plus® and Invivac® have been on the market in several European countries for a number of years.

Table 2. An assortment of vaccines available in the European Union

Disease	Registered Name	Company	Vaccine Composition	Type of Vaccine
Diphtheria,	dT reduct	Sanofi Pasteur	dT	toxoid
Tetanus,	Tdpur	Chiron	dT	toxoid
Pertussis	Polio Salk	Sanofi Pasteur	IPV	inactivated
and/or	Boostrix	GSK	dTaP	subunit (aP)
Poliomyelitis	Repevax	Sanofi Pasteur	dTaP-IPV	-
	Hexavac	Sanofi Pasteur	dTaP-HiB-Polio-HepB	-
	Infanrix-HiB+IPV	GSK	dTaP-HiB-IPV	-
	Infanrix Hexa	GSK		-
Hepatitis A	Avaxim	Sanofi Pasteur	*	inactivated
	Epaxal	Berna	*	virosome
	Havrix	GSK	*	inactivated
	Vaqta	Merck and Co	*	inactivated
	Twinrix	GSK	HepA+B	inactivated (HepA)
Influenza	Addigrip	Sanofi Pasteur	*	subunit + adjuvant
	Begrivac	Chiron	*	split-virus
	Fluad	Chiron	*	subunit + adjuvant
	Fluarix	GSK	*	split-virus
	Fluvirin	Chiron	*	subunit
	Fluzone	Sanofi Pasteur	*	split-virus
	Inflexal V	Berna	*	virosome
	Influvac Plus	Solvay	*	virosome
	Invivac	Solvay	*	virosome
	Sandovac	Sanofi Pasteur	*	subunit
	Vaxigrip	Sanofi Pasteur	*	split-virus
Pneumonia	Prevnar	Wyeth	*	7-valent conjugate
	Pneumo 23 "Merieux"	Sanofi Pasteur	*	23-valent conjugate
	Pneumovax 23	Merck and Co	*	23-valent conjugate
Tick-borne	Encepur	Chiron	*	inactivated whole virus
encephalitis	FSME immune	Baxter	*	inactivated whole virus
Varicella	Varilrix	GSK	*	live-attenuated
(Chickenpox)	Varivax II	Merck and Co	MMR-V	live-attenuated
Yellow fever	Stamaril	Sanofi Pasteur	*	live-attenuated
	YF-Vax	Sanofi Pasteur	*	live-attenuated
	Arilvax	Chiron	*	live-attenuated

aP, acellular pertussis; d, diphtheria; GSK, GlaxoSmithKline; HepA+B, hepatitis A+B; HiB, haemophilus influenzae B; IPV, inactivated polio virus; MMR-V, measles-mumps-rubella-varicella; T, tetanus; *, vaccine that protects only against the pathogen indicated under "Disease"; adapted from ref. 88.

They display a high immunogenicity and a similar safety profile in elderly persons compared with inactivated influenza vaccines.[16-18] Furthermore, new live-attenuated and subunit influenza vaccines are currently in clinical trials that promise to have an increased efficacy of protection (Table 1). Especially live-attenuated influenza vaccines are believed to elicit strong T-cell responses and should be able to enhance antibody levels after vaccination. Importantly, before administration of

live-attenuated vaccines to elderly or immunocompromised persons, an acceptable safety profile has to be demonstrated. Irrespective of the improvement of influenza vaccines for elderly persons, vaccination of children is clinically effective[19] and high vaccination coverage among pupils has demonstrated to induce herd immunity and to reduce mortality in older adults.

Pneumonia

Streptococcus pneumoniae is an important cause of invasive clinical manifestations such as bacterial pneumonia, meningitis and septicemia, particularly in young children and the elderly. 80 to 90% of deaths associated with *Streptococcus pneumoniae* infection occur in people aged 60 years and above. Several further groups at higher risk of invasive pneumococcal disease have been defined, including individuals with splenic dysfunction, immunosuppression, chronic pulmonary or cardiac disease, diabetes mellitus and chronic liver disease. Generally, antibiotic therapy has to be initiated as soon as possible to reduce the risk of complications due to pneumonia, meningitis or sepsis. Nonetheless, 50% of all deaths occur within the first 48 hours despite adequate antibiotic therapy. This may be due to the increased occurrence of multiple drug-resistant pneumococcal strains. In 2002, the proportion of penicillin-resistant *Streptococcus pneumoniae* was reported to be 53% in France and more than 25% in Israel, Poland, Romania and Spain.[21] After recovering from pneumococcal infection, people are not necessarily immune, because there are about 90 different serotypes and immunity will be guaranteed only to the strain that has caused the infection. Currently, pneumococcal vaccines are available that include up to 23 strains which are responsible to cause disease in almost 90% of all cases (Table 2). These vaccines offer protection against invasive pneumococcal disease in 65% of the general elderly population [22,23] whereas in elderly persons with high risk factors, the protective effect of vaccination seems to be only moderate. Although many European countries recommend the administration of pneumococcal vaccines to all those >65 years of age, vaccination coverage among the elderly population is very low. This may be due to the high costs of the vaccine and its unsatisfying efficacy in elderly people. But more immunogenic vaccines are currently in different phases of clinical trials (Table 1) and promise to be more efficient in old age. Additionally, implementing pneumococcal vaccination for children may decrease the incidence of pneumococcal disease in the elderly by reducing transmission and possibly accomplishing herd immunity.[24]

Tuberculosis

Each year, about 8 million people are infected worldwide with the tubercle bacillus *Mycobacterium tuberculosis* and 1.6 million of them die. The EU25 has a tuberculosis (TB) burden of more than 50,000 new cases per year, with the highest incidences in Latvia, Lithuania and Estonia (50-100 cases/100,000). The risk of developing a disease following TB infection is about 5-10% during lifetime and individuals above 65 years of age have a four-fold increased risk of developing TB than the average population.[25] TB is also frequently diagnosed with delay due to an atypical manifestation in old age. This may lead to an increased morbidity and mortality and to a spreading of the disease, in particular within institutionalized elderly persons.[26] Further difficulties include the increased emergence of new, multiple drug-resistant strains with higher transmissibility,[27] the poor efficacy of the current bacille Calmette Guérin (BCG) vaccine in protecting adults and elderly people from pulmonary infection[28] and the increased risk of TB co-infection in HIV positive patients.[29] However, in the past few years, several TB vaccine candidates have entered phase I clinical trials, including adjuvanted subunit vaccines as well as improved live recombinant strains of the current BCG vaccine (Table 1). All these vaccine candidates are supposed to induce an effective and sustainable cellular immune response which is thought to be crucial to protect the host from an intracellular pathogen such as *Mycobacterium tuberculosis*.[30]

Herpes Zoster

Primary infection with the Varicella zoster virus (VZV) causes chickenpox which is usually a mild disease in childhood. The virus then persists in a latent form in sensory ganglia until its

reactivation which results in the clinical manifestation of herpes zoster (shingles). Between 13 and 26% of persons with herpes zoster develop complications, such as postherpetic neuralgia.[31] Postherpetic neuralgia also increases with age with a prevalence of 50% in people aged 70 years and above. The incidence and severity of herpes zoster increase with age, because VZV reactivation is associated with a progressive decline in cell-mediated immunity to VZV.[32,33] Routine vaccination of children using a tetravalent vaccine that protects against measles, mumps, rubella and varicella will soon be available (Table 1) and may reduce the incidence of chickenpox as well as the reactivation of VZV in later life. Since 1995, a live-attenuated Oka strain VZV vaccine is on the market that has shown clinical efficacy in preventing children from chickenpox.[34] However, the currently available VZV vaccines have not been proven to adequately boost T-cell responses in older adults and to prevent reactivation of herpes zoster. Recently, a vaccine that may prevent herpes zoster virus reactivation has been submitted for registration. This live-attenuated VZV vaccine has been developed to prevent reactivation of herpes zoster in the elderly.[35,36] This is of particular importance, because the elderly population has not been vaccinated against but may have been frequently infected by VZV. For instance, more than 90% of adults in the United States have had chickenpox. As a consequence, it is estimated that up to 800,000 people in the United States suffer from shingles each year and the incidence is expected to increase as the population ages. Thus, reactivation of herpes zoster and its clinical manifestations represents a serious health burden to the growing elderly population and could be counteracted by potent vaccines.

Cytomegalovirus

The cytomegalovirus (CMV), a B-herpesvirus, has also been shown to persist throughout life until its reactivation as a result of immune suppression or deficiency. CMV infection is quite common and affects 60-100% of the adult population, depending on the area. The CMV is transmitted via person-to-person contacts but immunocompetent subjects mostly do not recognize infection as it causes no or few unspecific symptoms. However, a CMV infection represents a severe health problem in immunocompromised persons (e.g., due to immunosuppressive disease, chemotherapy or transplantation) or in a fetus as a result of congenital infection. Research results over the past decade suggest that CMV favors an accelerated aging of the immune system as CMV infection is chronic and the organism is forced to continuously prevent virus reactivation.[37-39] Despite the high frequency of CMV-specific CD8$^+$ T-cells, the virus usually can not be eliminated by the immune system. This is because the virus has evolved several mechanisms to escape the host's immune defense.[40] For instance, CMV encodes for a type of proteins called immunoevasins that modulate the presentation of viral peptides or directly suppress cellular immune responses. Hence, the accumulation of CMV-specific T-cells substantially constricts the diversity of the T-cell repertoire[41] and leads to the production of proinflammatory cytokines, such as gamma interferon and tumor necrosis factor alpha.[37] This imbalance in the cytokine production profile may not only promote the pathogenesis of age-related diseases[42] but leads to a decreased production of antibodies following influenza vaccination in elderly persons.[43] A few antiviral substances including ganciclovir, valganciclovir, foscarnet and cidofovir are available to prevent CMV infection in immunocompromised patients. But antiviral therapy is limited by its severe adverse reactions, such as neutropenia, nephrotoxicity, hypocalcemia and seizures. Another strategy is the adoptive transfer of donor-derived CMV-specific CD4$^+$ and CD8$^+$ T-cells that may restore the host's immunity against CMV.[44] Despite the need of a safe and potent vaccine that prevents CMV disease, no vaccine candidate has yet entered the market. A few vaccines against CMV are currently in phase I/II clinical trials (Table 1). Active immunization against CMV could reduce the incidence of neonatal infections as well as complications in immunocompromised persons and may prevent CMV-associated premature aging of the immune system when applied early in life.

Pertussis

Pertussis (whooping cough) is a highly contagious respiratory system infection caused by the bacterium *Bordetella pertussis* and rarely by *B. parapertussis, B. bronchiseptica* or other pathogens.

Each year, more than 20 million cases of pertussis are reported worldwide, 90% of which occur in developing countries, with an estimated 200,000 to 300,000 fatalities. The implementation of routine childhood vaccination against pertussis has reduced the high mortality rate among children. Although most infants are being immunized against pertussis in industrialized countries, immunity usually fades during adolescence. Consequently, a significant rise in pertussis incidence has been noticed in adolescents and adults.[45] However, the reported pertussis cases in adults and elderly people are likely to be underestimated because symptoms of disease may be characterless and make clinical diagnosis difficult. Among nonvaccinated elderly people the attack rate of pertussis is high (53%) and up to 10% of elderly persons may die from intracranial bleeding while they are symptomatic for pertussis.[46] Regular booster immunizations should thus be considered for adults and elderly persons, which is indispensable to remain protected from disease.

Tetanus and Diphtheria

Tetanus is acquired via environmental exposure to the spores of *Clostridium tetani*, which are present in soil worldwide. The disease is caused by a potent neurotoxin produced by the bacterium in dead tissue, e.g., dirty wounds. Diphtheria is a bacterial disease caused by *Corynebacterium diphtheriae* and is transmitted from person to person through close physical contact. The public health burden of both diseases has been low in developed countries due to routine immunization. However, outbreaks of diphtheria have been reported in the independent states of the former Soviet Union, Algeria, China, Iraq, Sudan, Thailand and other countries. Thus, maintaining high vaccination coverage is important to prevent the outbreak of new diphtheria epidemics. Although vaccines that prevent from tetanus and diphtheria have been used for routine immunization for a long time all over the world, few studies exist that document their efficacy in elderly people. The vaccination coverage among elderly subjects is decreasing in several European countries and up to 40% of appropriately vaccinated elderly persons do not have protective tetanus-specific antibody concentrations.[47-49] Therefore, public health authorities of some European countries have recommended five instead of ten year booster vaccination intervals for people over 60 years of age. Additionally, strategies should be developed to draw public attention to the problem of immunizations in the elderly, to inform general practitioners and to increase vaccination acceptance.

Travel Vaccines

The increasing mobility of elderly persons recognized worldwide is accompanied by an enhanced risk to encounter new antigens. This may be of concern because elderly persons possess a limited T-cell repertoire that may not guarantee full responsiveness to a wide variety of new antigens (see below for details). Nevertheless, in vitro experiments have demonstrated that naive T-cells from elderly persons can still be stimulated by neoantigens, at least to the recombinant Etr protein of TBE virus and rabies virus.[50] Based on an assessment of the risks for travel-related diseases, including the destination, the type of journey and the duration, vaccination is recommended to protect from typhoid and yellow fever, hepatitis A and B, Japanese encephalitis, tick-borne encephalitis (TBE) or rabies. But elderly persons should also check whether they have followed the recommended booster intervals of routine immunizations, e.g., against tetanus, diphtheria, poliomyelitis, measles or influenza.

TBE is caused by a virus that is primarily transmitted to humans by infected ticks. There are three genetically closely related subtypes of the TBE virus known (European, Siberian and Far Eastern subtype). TBE is among the most dangerous neuro-infectious diseases in Europe and Asia and is responsible for up to 12,000 cases of TBE annually, most of them occurring in Russia, Czech Republic and the Baltic states.[51] Up to 30% of adults with clinically confirmed TBE infection develop meningitis or meningoencephalitis and the lethality of TBE in Europe is up to 1%. Yet, there is no specific therapy available and, therefore, active immunization with inactivated whole virus provides the only efficient protection from TBE disease (Table 2).[52] Importantly, more and more TBE cases are reported in people over 50 years of age and vaccination coverage in this population is lower than average. Therefore, future strategies should increase the vaccination coverage among

elderly persons and assure that they stick to regular booster intervals. Anyhow, regular boosters should be given throughout life as this may favor the maintenance of long-lasting humoral immunity against TBE[53] and may decrease the risk of immunization failures in the elderly.

Hepatitis A is an acute disease of the liver caused by the hepatitis A virus (HAV), a nonenveloped virus belonging to the Picornaviridae family. Each year, an estimated 1.5 million cases of hepatitis A occur worldwide. HAV infection induces life-long immunity and is usually asymptomatic in young children, whereas adults frequently experience symptomatic disease. HAV is acquired directly from infected persons by close contact or by the consumption of contaminated drinking water, vegetables, fruits or shells. HAV vaccination is recommended when traveling to tropic and subtropic countries that have an increased risk of infection. For instance, the risk of hepatitis A infection of persons traveling to developing countries was estimated to be 3 to 20 cases per 1000 persons per month of stay, varying with destination, living conditions and age.[54] Improved sanitary standards in developed countries have reduced the opportunity for environmental exposure to HAV and have lowered the overall incidence of infection. Paradoxically, susceptibility to the virus increased because of the decrease in natural immunity. Consequently, less than 20% of persons born after 1945 have a natural immunity against HAV.[54] In contrast to hepatitis B and C that may lead to the manifestation of a chronic infection, clinical illness after hepatitis A infection is usually mild in young individuals. But increasing age represents an enhanced risk of severe infection and mortality rates are about 2% for persons over 40 and 4% for those over 60 years of age.[54] Several vaccines against hepatitis A are available (Table 2) and a study of 773 adults showed that immunogenicity and safety profiles between Twinrix* and Havrix* are comparable.[56] But there is some evidence of lower antibody titers with advanced age. For instance, the seroconversion rates 8 months after two doses of Havrix* were found to be 85% and 60% for adults < 35 years and >35 years, respectively.[57] After the recommended immunization schedule with Twinrix*, seroprotection was 92% and 63% for adults <40 years and >60 years, respectively.[58] Therefore, it may be useful to measure HAV antibodies in elderly persons, as in the case of vaccination failure, boosters have shown to be effective.[58] It is further recommended that the vaccine is given at least 3 to 4 weeks before travel due to a slower onset of the antibody response in elderly individuals.[59]

Another travel vaccine is directed against yellow fever (YF), which is endemic in tropic regions of Africa and South America. YF is transmitted by the bite of infective Aedes aegypti and other mosquitoes that bite during daylight hours in regions below 2500 meters of altitude. Most infections lead to an acute illness characterized by fever, muscular pain, headache, anorexia, nausea and/or vomiting, often with bradycardia. After a few days, about 15% of patients progress to a second phase, with resurgence of fever, development of jaundice, abdominal pain and haemorrhagic manifestations. Half of these persons die 10-14 days after the onset of illness. The WHO estimates that a total of 200,000 cases of YF occur each year, with about 30,000 deaths.[60] YF also represents a significant risk to more than 3 million travelers that visit YF-endemic areas each year. Neonates and elderly individuals demonstrate the highest mortality when infected by the YF virus. As there is no specific antiviral treatment against YF available yet, vaccination is the only way to protect persons from YF disease. The currently available vaccine contains a live-attenuated 17D strain virus (Table 2) and has been shown to be safe and highly potent.[61] However, due to the increased use in international travelers, it has become evident that advanced age might be a risk factor for serious adverse effects and even death.[62] Compared with persons aged 25-44 years, individuals aged <75 had an 18-fold greater risk to experience serious adverse events after vaccination. The rate for systemic illness requiring hospitalization or leading to death after YF vaccination was reported to be 3.5 per 100,000 among people 65 to 75 years of age and 9.1 per 100,000 for people more than 75 years. Furthermore, there are no studies available that demonstrated the efficacy of the YF vaccine in elderly persons. Accordingly, recommendations and manufacturing standards have been modified to increase vaccine safety in elderly persons. Although the benefit-risk ratio still favors the vaccination of people at high risk for infection and outlines the vaccine's fundamental role in disease prevention and control, efforts to improve safety and to ensure vaccine efficacy in elderly persons are of urgent need.

How Does Immunosenescence Influence Vaccine Efficacy?

The term immunosenescence refers to a complex remodeling of the immune system in old age and may contribute significantly to morbidity and mortality in the elderly. Thymic involution, telomere shortening, T-cell signal transduction changes, alterations in the interaction of the innate and adaptive immune response, impaired DNA repair and antioxidant mechanisms as well as persistent antigenic stress may all be factors contributing to immunosenescence. Although perturbations of innate immune system components have been described, much of the decrease in immunoresponsiveness seen in elderly people is associated with changes in T-cell responses. This is due to the continuous loss of functional thymic tissue with increasing age.[63,64] The thymus, the central lymphoid organ, is responsible for the maturation and selection of so-called naive T-cells that regenerate the peripheral T-cell pool and retain the capability of the immune system to respond to a variety of different pathogens. In old age, the number of naive T-cells decreases while the number of antigen-experienced T-cells increases.[65,66] These antigen-experienced T-cells include a substantial proportion of senescent memory-effector T-cells that accumulate in elderly persons. Senescent memory-effector T-cells display phenotypic (loss of costimulatory molecules such as CD28 and CD40L) as well as functional changes (altered cytokine production profile, decreased proliferative response, shortened telomeres, increased resistance to programmed cell-death and restricted T-cell diversity).[67,68] Of particular importance, the senescent $CD8^+CD28^-$ memory-effector T-cell population predominantly produces the pro-inflammatory cytokine gamma interferon (IFNγ), but does not produce interleukin 2 (IL-2) and the anti-inflammatory, B-cell stimulating cytokine IL-4.[43] Recent data also support the hypothesis that chronic infection with the cytomegalovirus, a β-herpesvirus, may lead to a decrease in the size of the naive and early memory $CD8^+$ T-cell pool, but to an increase in the number of dysfunctional, IFNγ-producing $CD8^+CD28^-$ memory-effector T-cells (Fig. 2).[37] One clinical consequence of the accumulation of $CD8^+CD28^-$ T-cells is an impaired generation of protective antibody levels after vaccination.[43,69] Furthermore, the age-dependent increase in the level of pro-inflammatory cytokines may lead to ubiquitous chronic inflammatory responses in old age[42] and may therefore support the development of age-related chronic diseases, such as atherosclerosis,[70] rheumatoid arthritis[71] and Alzheimer's disease.[72,73]

Although individuals maintain a relatively constant total number of peripheral B-cells during aging, each B-cell subset comprises severe perturbations in size, dynamics and repertoire. The alterations affecting the B-cell subsets are due to a decreased generation of B-cell precursors, such as early lymphoid precursors and pro-B-cells. Cell-intrinsic as well as micro-environmental disturbances are both likely to contribute to the decreased output of pro-B-cells. Furthermore, alterations in environmental factors also impair overall V(D)J recombinase activity among pro-B-cells[74] which accounts for the limited B-cell repertoire frequently detected in elderly persons.[75] Although no decrease in overall serum immunoglobulin levels have been observed during aging, the antibodies generated in old age are of lower affinity due to a shift in antibody isotypes from IgG to IgM.[76] Of particular importance, B-cells from elderly individuals are stimulated 70% less efficiently by follicular dendritic cells than B-cells from young subjects,[77] suggesting loss of B-cell function, in part due to the decreased expression of costimulatory molecules, such as CD40 or CD27.[78] Impaired T-cell-mediated immunity as well as defects in antigen presentation by antigen presenting cells (APC) also contribute to the decline in B-cell specific functions.[79]

To summarize, environmental factors as well as intrinsic alterations lead to the disturbance of the peripheral B-cell pool characterized by the loss of B-cell costimulatory molecules and loss of B-cell diversity. The cytokine environment as well as T-cell-mediated B-cell stimulation are further important determinants of intact antibody production.[65] Thus, decreased numbers of $CD28^+$ and $CD40L^+$ T-cells and a lack of cytokines such as IL-2 and IL-4, are both likely to endanger normal T-cell/B-cell communication, B-cell growth, differentiation and antibody production in the elderly.
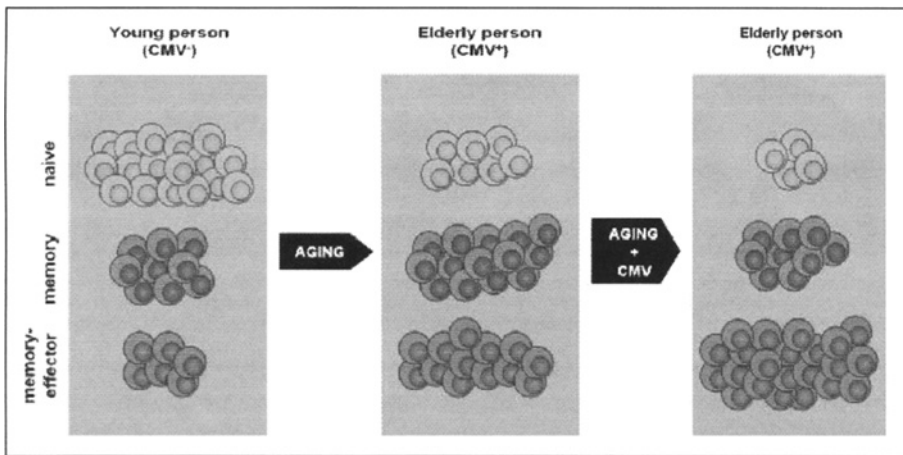
Figure 2. Schematic representation of the effects of age and persistent CMV infection on the peripheral CD8+ T-cell compartment. The number of naive CD8+ T-cells declines with age due to thymic involution whereas antigen-experienced CD8+ T-cells, such as memory and effector-memory cells increase. Persistent CMV infection leads to a further accumulation of senescent and dysfunctional memory-effector CD8+ T-cells. The exact percentage of the various CD8+ T-cell subsets was determined in ref. 37.

How to Improve Vaccine Efficacy in Old Age?

There is a tremendous need to increase the protective effect of vaccines in the elderly. Research of the last decade has provided new insights into the molecular mechanisms of the immune response in old age, which can now be used for the development of potent vaccines. In the past, vaccines were primarily designed to elicit a strong humoral immune response. However, vaccines in elderly persons may be more effective if the stimulate innate immune components and the generation of long-lived memory T-cells. Currently, several strategies are being pursued to increase immunogenicity, to minimize adverse side effects and to increase vaccine acceptance by introducing needle-free injection devices. Proven and promising vaccine technologies are used to design conjugate, subunit, live vector, DNA and live-attenuated vaccines (Table 3).[80] While live-attenuated vaccines (e.g., against varicella, measles or yellow fever) stimulate numerous immune components and display enhanced immunogenicity, conjugate and subunit vaccines (e.g., against influenza) are often supplemented with adjuvants[81] to ensure their protective effect. Generally, adjuvants can be divided into antigen delivery systems (cationic microparticles, proteasomes and virus-like particles) and immune potentiators (e.g., cytokines). These adjuvants may overcome the proposed age-related functional decline of innate immune responses by targeting pattern-recognition receptors, such as the recently identified toll-like receptors or nucleotide-binding oligomerization domain proteins.[82] The enhanced activation of the innate immune system may also improve antigen processing and presentation leading to more potent T and B-cell responses and to sustained immunological memory. Vaccines supplemented with the DNA of cytokines (e.g., IL-2, IL-7, IL-12, IL-15 or IL-21), chemokines or costimulatory molecules may magnify immune responses by generating more and long-lived memory T-cells[83-85] and may overcome immunodominance.[86]

In addition to improve vaccine efficacy, a modification of vaccination strategies for elderly persons has been supported by the results of several vaccination trials. For instance, a decreased response and a shortened duration of protective immunity following booster immunization is a characteristic feature of old age.[87] Thus, several European health authorities have recommended five-year vaccination intervals for tetanus, diphtheria, pertussis and pneumonia. Increased public awareness of regular booster vaccinations in adults should be enforced, as these immunization

Table 3. Attributes of different vaccine types

Category	Advantages	Disadvantages
Conjugate vaccines	High clinical tolerability	Booster immunizations usually required; no CTL responses
Inactivated whole-virus vaccines	High antibody levels	Higher probability of adverse side effects compared to subunit or conjugate vaccines (e.g., replacement of whole-cell pertussis vaccine by acellular pertussis vaccine)
Live-attenuated vaccines	Booster immunizations usually not required; high antibody levels and strong CTL responses	Safety concerns for immunocompromised persons
Live-vector vaccines	Booster immunizations usually not required; high antibody levels and strong CTL responses	Moderate safety concerns for immunocompromised persons
DNA vaccines	Specific manipulation of the cellular immune response; increased efficiency when added to subunit vaccines	Low immunogenicity
Subunit vaccines	High clinical tolerability due to the high purity of single immunogenic peptides only	Moderate immunogenicity can be overcome by supplementation of an adjuvant or DNA
Nonliving antigen delivery systems (e.g., virosomes, liposomes, virus-like particles)	High clinical tolerability; higher antibody levels and moderate CTL responses; delivery of a variety of purified antigens but also DNA	Biostability?

CTL, cytotoxic T-lymphocyte

regimes may be essential to maintain the ability to respond to recall antigens in old age. Recent results also indicate that long-lasting protection but also a good booster effect can be expected even a long time after the last vaccination, when a live-attenuated vaccine (e.g., polio vaccine) is used for primary immunization in early life. New delivery systems that make use of tiny micro-needles or non-injectable application devices (nasal, oral, transcutaneous) may further increase vaccination acceptance, especially in the case of influenza as this vaccination has to be repeated annually.

Conclusions

Infectious diseases in elderly persons are becoming an increasingly important issue. An utmost need represents the development of more immunogenic vaccines for the elderly. The improvement of specific vaccine types regarding immunogenicity and tolerability, the addition of adjuvants, the design of new delivery systems as well as specific immunization regimes should all contribute to an enhanced efficacy of vaccines in elderly persons. Further improvements may comprise the adjustment of vaccination intervals in old age, the increase in vaccine acceptance and vaccination

coverage as well as raising people's awareness to stick to the recommended booster vaccination intervals throughout life. In the distant future, vaccines may also play an important role in treating non-infectious diseases such as allergy, autoimmunity, Alzheimer's disease and cancers.

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