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Differential Approaches for Vaccination from Childhood to Old Age

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Abstract
Primary prevention strategies, such as vaccinations at the age extremes, in neonates and elderly individuals, demonstrate a challenge to health professionals and public health specialists. The aspects of the differentiation and maturation of the adaptive immune system, the functional implications of immunological immaturity or immunosenescence and its impact on vaccine immunogenicity and efficacy will be highlighted in this review. Several approaches have been undertaken to promote Th1 responses in neonates and to enhance immune functions in elderly, such as conjugation to carrier proteins, addition of adjuvants, concomitant vaccination with other vaccines, change in antigen concentrations or dose intervals or use of different administration routes. Also, early protection by maternal vaccination seems to be beneficial in neonates. However, it also appears necessary to think of other end points than antibody concentrations to assess vaccine efficacy in neonates or elderly, as also the cellular immune response may be impaired by the mechanisms of immaturity, underlying health conditions, immunosuppressive treatments or immunosenescence. Thus, lifespan vaccine programs should be implemented to all individuals on a population level not only to improve herd protection and to maintain protective antibody levels and immune memory, but also to cover all age groups, to protect unvaccinated elderly persons and to provide indirect protection for neonates and small infants.

Introduction

The demographic profile has dramatically changed in industrialized countries over the last decades. There are increasing survival rates of preterm infants with a relative immature immune system setting them at risk to acquire infectious diseases. At the other age extreme, the geriatric population is growing with a wide heterogeneity in health states among the elderly. A high number of adults surviving into late life suffer from lifestyle-associated and chronic diseases with treatments compromising their immune system and making them prone to complications of vaccine-preventable infectious diseases. But also intrinsic changes caused by the physiological aging of the immune system (immunosenescence) influence their susceptibility to infectious pathogens.

Primary prevention strategies, such as vaccinations at the age extremes, in neonates and elderly individuals,

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demonstrate a challenge for health professionals, public health specialists and decision makers. One idea is that approaches which may enhance the immune response to vaccine antigens in small infants with their relatively immature immune system may also apply to old people with a senescent immune system. Although this may be true in part, the present review aims to compare and contrast the immune response to vaccines at the beginning and the end of the lifespan showing similar and different features between an immature and a senescent immune system. The aspects of the differentiation and maturation of the adaptive immune system, the functional implications of immunological immaturity or immunosenescence and its impact on vaccine immunogenicity and efficacy will be highlighted in this review.

Age-Associated Changes of the Immune System

The immune system undergoes differentiation and maturation from prenatal life to old age with different implications for the defense against infectious diseases and inflammatory conditions, and is mainly seen as a process of specialization of the humoral and cellular reaction to chronic antigen stimulation with advancing life [1].

Age-Associated Changes of the T Cell System

Characteristics of the Neonatal T Cell System

Post-thymic maturation and homeostatic control of T cell generation by peripheral expansion of recent thymic emigrants (RTE) ensure T cell function and self-tolerance. Distribution of T cell subpopulations and absolute lymphocyte numbers undergo significant alterations depending on gestational age and maturity of neonates [2, 3] (table 1).

Th1-mediated responses, such as IFN-γ release and cytotoxicity, are developed soon after birth [4]. In preterm neonates, a higher susceptibility to viral infections was attributed to a relatively impaired IFN-γ production by γδ T cells within the first month of life [5].

A significant Th2 bias with production of IL-4, IL-10 and IL-13 was described in preterm and term infants, and was explained by a delayed maturation of an IL-12-producing dendritic cell subset [6].

Characteristics of the Aged T Cell System

Complex modifications of the T cell generation are seen in the thymus during aging and longevity with a decrease in thymic function and changes in the composition of the peripheral T cell pool [7] (table 1). Thymic involution results in a continuing decrease of RTE, characterized by lower T cell receptor (TCR) excision circles and CD31-expressing CD4+ T cells [7]. Despite lower numbers of naive T cells, mechanisms of T cell homeostasis attempt to maintain the peripheral T cell pool at a constant level, but may result in an abundance of terminally differentiated T cells and replicative exhaustion of effector memory T cells presenting markers of replicative senescence. Thus, T cell aging is characterized not only by phenotypic but also functional changes with a highly restricted TCR repertoire and less sufficient T cell help for B cell differentiation due to decreased IL-2 production [8]. Chronic antigen stimulation, e.g. by cytomegalovirus infection, is also proposed to be a driving factor of T cell senescence [1].

Several approaches have been undertaken to enhance thymic function in aged individuals via inhibition of atrophic factors, such as sex steroid or TGF-β inhibition, thymic rejuvenation by administration of stimulatory factors, e.g. IL-7, or by growth hormone-mediated pathways [9].

Similarities and Differences between Neonatal and Aged T Cell System

Table 1 compares and contrasts the features of the T cell system at the age extremes. Thymus function critically contributes to the diminished output of RTE in preterm infants and elderly persons [7]. Thymic size and structure seem to play a major role in the susceptibility to infectious diseases and affect the components of the peripheral naive T cell pool, which undergoes already significant homeostatic control in neonates [2, 3]. Whereas neonates have low fractions of memory T cells, but increased regulatory T cells, although with less suppressive function in preterm neonates, and an unrestricted TCR repertoire, elderly persons demonstrate high proportions of terminally differentiated T cells with loss of TCR diversity (table 1) [1, 7].

Age-Associated Changes in the B Cell System

Characteristics of the Neonatal B Cell System

In preterm neonates, B cells are generated to a similar extent as in term neonates and infants. However, a preferential neonatal B cell differentiation towards memory B cells rather than plasma cells was confirmed by a diminished IgG response and an impaired persistence of antibodies to both polysaccharide and protein antigens [10, 11] (table 1). The inadequate response to polysaccharides is explained by low expression of CD21 (comple-

Table 1. Immunological features in preterm infants, term neonates and elderly persons

Preterm infants	Term neonates	Elderly
T cells – Lower naive T cell counts – Reduced thymic growth – Reduced thymic size (depending on infectious diseases) – High turnover rates of naive T cells – Impaired IFN-γ production by γδ T cells – Diminished IL-7 levels – Reduced suppressive activity of regulatory T cells (Tregs) – Reduced natural killer cell activity	*T cells* – Homeostatic control of peripheral expansion of RTE – Elevated IL-17-producing T cells – Th2 bias (production of IL-4, IL-10, IL-13) – Delayed maturation of IL-12-producing dendritic cells – Higher proportions of circulating Tregs – Lower fractions of memory CD4+ T cells	*T cells* – Decrease in thymic function and RTE – Lower T cell receptor excision circles – Lower CD31-expressing CD4+ T cells – Lower numbers of naive T cells – Abundance of terminally differentiated T cells – Replicative exhaustion of effector memory T cells – Highly restricted T cell receptor repertoire – Less sufficient T cell help for B cell differentiation – Decreased IL-2 production
B cells – Preferential neonatal B cell differentiation towards memory B cells – Diminished IgG response – Diminished persistence of antibodies to both polysaccharide and protein antigens	*B cells* – Low expression of CD21 (complement receptor 2) – Delayed onset of antibody response – Lower peak levels and shorter persistence of antibodies – Lower IgG2 isotypes – Lower antibody affinity – Limited affinity maturation under 4–6 months of age – Reduced heterogeneity – Inability to respond to thymus-independent type 2 antigens (e.g. polysaccharides)	*B cells* – Age-dependent decrease in naive B cells – Blockade of early hematopoietic progenitors and B cell precursor maturation – Decreased expression of costimulatory molecules (e.g. CD27, CD40) – Loss of the diversity of the B cell receptor repertoire – Less B cell expansion – Reduced size of germinal centers – Dysregulation in interaction with other immune cells – Shift in antibody isotypes from IgG to IgM – Poor IgG responses to protein antigens, most polysaccharide antigens and decreased persistence of IgG antibodies

ment receptor 2) on neonatal and infantile B cells. Infants demonstrate a limited IgG affinity maturation under 4–6 months of age [11].

The placental transfer of maternal IgG antibodies is effective in protecting neonates and infants from infectious pathogens in early life, but depends on gestational age, maternal antibody concentrations, IgG subclasses, the nature of the antigen and placental characteristics [12].

Characteristics of the Aged B Cell System

Naive B cells show a pronounced age-dependent decrease mostly due to blockade of early hematopoietic progenitors and B cell precursor maturation [10] (table 1). During aging, a loss of B cell function is caused by decreased expression of costimulatory molecules, such as CD27 or CD40 [10]. In aged individuals, B cells also show a loss of the diversity of the B cell receptor repertoire and less B cell expansion, a reduced size of germinal centers and a dysregulation of interaction with other cell types of the immune system [1].

Although overall serum Ig concentrations stay remarkably stable during aging, a shift in antibody isotypes from IgG to IgM occurs causing lower affinity. In the elderly, poor IgG responses to protein antigens, most polysaccharide antigens and decreased persistence of IgG antibodies have been described [10].

Similarities and Differences between Neonatal and Aged B Cell System

Table 1 compares and contrasts the features of the B cell system at the beginning and the end of the lifespan, showing similar patterns of diminished antibody responses between both age extremes with low IgG antibody concentrations after contact with protein and polysaccharide antigens, decreased persistence and delayed affinity maturation, the latter particularly in neonates and small infants [10, 11]. Loss of B cell receptor diversity and decreased numbers of naive B cells contribute to the changes in the elderly (table 1) [10, 11].

Response to Vaccinations in Neonates and in the Aged Population

Neonatal Vaccination

Three vaccines against poliovirus (oral vaccine, OPV), hepatitis B virus (HBV) and Bacille Calmette-Guérin (BCG) are currently administered at birth in many countries worldwide and show a tolerable safety and efficacy profile [11]. Protection against the early-life disease burden of encapsulated bacteria, such as *Haemophilus influenzae* type b (Hib) or *Streptococcus pneumoniae*, causing life-threatening invasive disease, is highly desirable. Also, neonatal pertussis vaccination or influenza vaccination in pregnant women are proposed strategies to limit severe disease in this most vulnerable population.

Poliovirus Vaccination

Thanks to OPV administration at birth, 70–100% of neonates develop local intestinal immunity, and 30–50% demonstrated serum antibodies to at least one of the three OPV types, despite the presence of maternal antibodies [11, 13]. Preterm infants were also able to create a poliovirus-specific T cell response to the inactivated poliovirus vaccine comparable to those of term infants, but showed a diminished poliovirus-specific lymphoproliferation with also lower serotype 1 antibody levels [14].

Hepatitis B Vaccination

Hepatitis B immunoglobulin (HBIG) and HBV are administered concomitantly in neonates at risk of mother-to-child transmission of HBV. A seroconversion was seen only in 10–20% of infants vaccinated at birth. But also in the absence of HBIG administration, HBV vaccination alone was 70–80% effective in preventing disease transmission in this age group [15]. A lower increase in anti-HBs in neonatally vaccinated infants born to HBs antigen-positive mothers compared to infants who received the first dose at 2 months was explained by interference of maternally derived antibodies or insufficient maturation of the neonatal immune system [15].

BCG Vaccination

Given the risk of disseminated BCG disease in immunodeficient infants, the WHO recommends the BCG vaccine only in countries with a high burden of tuberculosis. However, several candidates to improve the BCG vaccination or replace it are currently under investigation in clinical trials [16].

Hib Vaccination

For prevention of infections with encapsulated bacteria, such as Hib, *Pneumococcus* or *Meningococcus*, polysaccharide and conjugate vaccines are available. With conjugation of a polysaccharide to a protein carrier, a sufficient T cell help for B cell responses is mounted and allows B cells which have been stimulated by polysaccharides to induce immunological memory. This is of importance in infants which are not able to create a memory response to polysaccharides [17]. In contrast to vaccination with plain polysaccharides, administration of conjugate vaccines against Hib increases the IgG production and the IgG:IgM ratio on repeated vaccination with predominance of IgG1 subclass and highly sufficient avidity maturation in young infants [18].

Besides expected advantages of conjugate vaccines in small infants, experiences with conjugate vaccines in neonates are rare and are based only on small studies. Antibody production was seen in 4-month-old infants who were vaccinated with tetanus-toxoid or modified diphtheria (CRM_{197} protein)-conjugated Hib vaccines at neonatal age [19]. However, neonatally primed infants who had only one dose showed lower antibody levels than infants immunized with two doses at birth and at 2 months [19].

Pneumococcal Conjugate Vaccination

Although small children are at high risk of suffering from invasive pneumococcal disease, the efficacy of pneumococcal vaccination in neonates is rarely investigated. Neonatal immunization with pneumococcal conjugate vaccine has been shown to increase the avidity of IgG antibodies directed against certain serotypes, which may reflect neonatal priming, but did not influence specific IgG levels or nasopharyngeal carriage compared to the infant control group [11]. In a cohort of Papua New Guinean infants who were vaccinated with 7-valent pneumococcal conjugate vaccine at birth and 1 and 2 months, an enhanced Th2, but not Th1, cytokine response to CRM_{197} was shown compared to infants who received the vaccine at 1 and 2 months of age only [20].

Meningococcal Conjugate Vaccination

Conjugate vaccines against meningococcal serogroups A, C, W-135 and Y have been shown to be immunogenic in children and adolescents with a similar serum bactericidal antibody (SBA) response in premature infants compared to term infants [21]. In mice, protective SBA levels were produced by neonatal administration of a meningococcal serogroup C conjugate vaccine using CRM_{197}, encouraging neonatal immunization strategies in humans

[22]. Interestingly, concomitant administration of BCG enhances the antibody response to meningococcal serogroup C conjugate vaccine in neonatal mice, probably by promoting Th1 responses [22].

Influenza

Neonates and small infants have a high risk to suffer from severe influenza-associated illness due to their lack of prior exposures to the influenza virus and their reduced immune responsiveness which is probably caused by their tendency to preferentially develop type 2 immune responses with less activation of IFN-γ-specific responses and cytotoxic activity of T cells [4–6].

Maternal immunization against influenza and, thereby, protecting the offspring indirectly by placental transport of specific IgG demonstrates a new aspect of neonatal protection [12, 23].

Pertussis

Preterm infants as well as full-term infants are at high risk of *Bordetella pertussis* infection associated with higher morbidity and mortality, because no immunity exists against pertussis infection at this age. In preterm infants, antibody responses to pertussis vaccine antigens were reported to be lower or similar to those developed by term infants [11]. Most preterm infants are able to mount a pertussis-specific cellular IFN-γ response after the first doses of an acellular or whole-cell pertussis vaccine [24].

A prospective aspect of protecting small infants against pertussis, tetanus and diphtheria is vaccination of pregnant women [25], which seems to be well tolerated and inducing placental transport of specific antibodies, which is almost mediated by the neonatal Fc receptor [12].

Vaccination in the Elderly

Current guidelines for vaccination of elderly promote the preventive aspects related to life-threatening diseases, such as influenza, pneumococcal pneumonia and tetanus/diphtheria, and diseases with high morbidity and impairment of life quality, such as pertussis and herpes zoster [26]. Perceiving the individual risk of older persons, also vaccines against hepatitis A and B, meningococcal disease and tick-borne encephalitis (TBE) should be considered. However, the senescent immune response to vaccines remains a challenge to physicians, public health strategies and the development of new vaccines [27].

Influenza Vaccination

The increased severity and mortality of influenza in aged people are seen as a consequence of a diminished T cell-mediated immunity and a defective antigen presentation resulting in a decline of IFN-γ-producing influenza-specific cytotoxic effector T cells and antibody production [1]. Influenza vaccination induces circulating antibody-secreting plasmablasts, defined by their expression of CD19+CD38++CD27++, with a peak around day 7 after immunization. The frequency of vaccine-specific plasmablasts and the concentration of plasmablast-derived polyclonal antibodies were lower in elderly than in young individuals, whereas the yields of secreted IgG per plasmablast and the vaccine-specific IgG avidity were similar [28]. Reduced T cell functions, age-related B cell defects and a diminished class switch recombination of antibody isotypes resulting in lower antibody responses characterize the impaired humoral and cellular immune response to influenza vaccination in elderly persons [29]. A recent report demonstrated that preexisting CD4+, but not CD8+, T cells respond to influenza internal proteins, which was associated with lower virus shedding and less severe illness [30].

In aged adults, a differential response to influenza vaccine was also seen depending on their inflammatory potential, e.g. mediated by elevated serum IL-6 levels [31]. The role of the innate immune system and its age-associated changes, such as reduced macrophage and neutrophil activation, reduced NK cell function and diminished activation through Toll-like receptors with less upregulation of the costimulatory molecule CD80, in influenza-specific immune responses compared to younger individuals are still matter of debate [31].

Influenza vaccination seems to have a large effect on preventing pneumonia, reducing hospital admissions and preventing all-cause mortality [32, 33]. However, some bias in the effectiveness was discussed in adults aged >70 years, as exclusion of elderly with fragile health or nursing home residents, the use of non-specific outcomes (e.g. all-cause death), inclusion of the advocated indirect effects of vaccinating health care workers or co-administration with pneumococcal vaccines may distort the effectiveness of influenza vaccine studies in elderly persons [33] (table 2). Several open questions regarding influenza vaccination in the geriatric population remain, such as whether pre-vaccination antibodies may influence the vaccine response, whether the innate immune system may influence the specific immune response and how age-related expansions of dysfunctional terminally differentiated T cells affect the success of the vaccination, as so far a correlate of protection against clinically symptomatic infection was only demonstrated for antibodies [33].

Table 2. Concepts to improve protection against vaccine-preventable diseases

Immunological aspects	Study aspects	Public-health aspects
– Application routes (e.g. intradermal injection, intranasal application) – Higher antigen dose – Vaccines with adjuvants (e.g. cationic liposome complexes, TLR ligands, cytokines, virosomes, MF59) – Conjugated vaccines or use of live attenuated vaccines – Coadministration of cytokines promoting Th1 responses – Concomitant administration of other vaccines (e.g. BCG) – Thymic rejuvenation (e.g. by TGF-β inhibition, by growth factors, IL-7) – Timing of the first dose and booster intervals, repeated vaccination	– Definition of end points and outcomes (e.g. clinically defined disease, laboratory-confirmed disease, disease-associated hospital admission, disease-associated mortality, all-cause mortality) – Definition of immunogenicity (e.g. humoral or cellular immune response) – Definition of epidemiological terms (e.g. efficacy, effectiveness) – Definition of biomarkers (e.g. for immunosenescence) – Definition of risk profiles (e.g. for chronic inflammation) – Inclusion of confounders (e.g. frailty, nursing home residents, immunosuppressive drugs, hormonal changes, gender aspects, psychosocial stress, chronic inflammation, malnutrition, coadministration of other vaccines, pre-immunization antibodies, maternally derived antibodies) – Conduction of a randomized, placebo-controlled trial over several seasons	– Vaccination of close contact persons (e.g. health care professionals) – Herd protection (e.g. population based) – Accessibility and distribution of vaccinations (e.g. for nursing home residents) – Public funding, socioeconomical aspects – Lifespan vaccine programs

Tetanus, Diphtheria and Pertussis Vaccination

It is generally recommended to immunize persons aged ≥65 years with tetanus, diphtheria and acellular pertussis vaccine due to their waning immune response and lack of wild-type boosting [26]. For tetanus-toxoid, a significant impact of the time of the last vaccination, age and the pre-booster titers have been shown, with a better effect if pre-booster antibody concentrations were high.

Meningococcal Vaccination

Sufficient immunogenicity for conjugate meningococcal vaccines with maintenance of antibodies was suggested for persons >55 years [34]. In this age group, the T cell-dependent immune response achieved by coupling the bacterial polysaccharides to a carrier protein should increase immunogenicity of the vaccine and provide long-term persisting immunity, and is also able to reduce nasopharyngeal carriage essential for herd protection. However, conjugate vaccines are often not licensed for older age groups and are rarely used in aged individuals; thus, experience with conjugate vaccines and their impact on humoral and cellular immunity against vaccine-preventable diseases in the geriatric population is still unclear [34].

Pneumococcal Vaccination

Considering not only the impact of influenza on the incidence of pneumonia in the elderly, the pneumococcal vaccination with the 23-valent polysaccharide vaccine (PPV23) is strongly recommended in adults aged ≥65 years. PPV23 has been shown to prevent invasive pneumococcal disease (e.g. bacteremia) with evidence for both the efficacy and effectiveness with similar problems as for estimating the effectiveness of influenza vaccination [32, 33] and a so far unclear effect on the reduction in the all-cause mortality rate [35] (table 2). There is a current controversy surrounding pneumococcal vaccination in the elderly. The Joint Committee on Vaccination noted that no discernible decrease in the incidence of invasive pneumococcal disease in people aged ≥65 years following the introduction of the PPV23 in England and Wales was observed despite the widespread use of PPV23 in this age group [35]. However, the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) into the childhood vaccination program in 2006 reduced invasive pneumococcal disease in the elderly with an expected further decline of vaccine serotypes by introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) [35]. So far, no conclusive evidence for the effectiveness of PCV13 in adults exists, although the conjugate vaccine is believed to be more immunogenic [35].

For many pneumococcal polysaccharide serotypes and meningococcal polysaccharides, the phenomenon of hyporesponsiveness (immune tolerance) was observed. Hyporesponsiveness may also have clinical implications for the introduction of polysaccharide vaccines into a conjugate vaccine schedule or repeated vaccinations with polysaccharide vaccines [17]. To date, hyporesponsiveness was not shown for conjugate vaccines except, possibly, for pneumococcal serotype 3.

Hepatitis B Vaccination

Hepatitis A and B vaccination is recommended for persons at risk to acquire these infections. Although data about the persistence of protective antibody levels against hepatitis A or for anti-HBs in older people are rare, long-term immunogenicity of the combined hepatitis A and B vaccine was demonstrated up to at least 15 years after primary vaccination in subjects aged 17–43 years [15].

TBE Vaccinations

Depending on lifestyle factors and living in endemic areas, vaccination against TBE is recommended. As older people tend to reach lower antibody titers against TBE than younger individuals and titers decrease earlier, they should have their first TBE booster vaccination no later than 3 years after complete primary immunization [36]. Individuals with very low pre-booster antibodies for TBE vaccine also showed a low booster effect [36].

Varicella-Zoster Virus Vaccination and Zoster Vaccination

Vaccination against varicella-zoster virus (VZV) has been shown to be well tolerated and beneficial in children. However, by introduction of the VZV vaccine, disease models predict an increase in primary VZV cases in adolescence and young adults with higher complication rates and an increase in herpes zoster (shingles) due to less chance of wild-type virus boosting [37]. However, so far, the increasing incidence of herpes zoster cases in the United States could not be correlated with the VZV vaccine coverage rate, and may be influenced by so far unknown epidemiological factors [37].

Reduced VZV-specific cellular effector mechanisms have been described to increase the risk of VZV reactivation in persons aged >55 years with risk of life-threatening disseminated disease, high morbidity due to superinfections and impairment of life quality by postherpetic neuralgia, while levels of VZV-specific antibodies have less impact on the protection against reactivation or symptomatic disease after VZV reexposure [38]. The rationale for vaccinating aged individuals with high VZV antigen-containing live attenuated zoster vaccines (14-fold more plaque-forming units of the lyophilized Oka-VZV strain than varicella vaccines) is based on the finding that exposure to wild-type VZV as well as asymptomatic reactivations may boost the cellular immune response and, thus, prevent symptomatic disease [39]. Overall, the effectiveness of the herpes zoster vaccine has been demonstrated in a 66.5% reduction in the incidence of postherpetic neuralgia and a 51.3% reduction in the incidence of herpes zoster [39]. However, still many questions about the usefulness of herpes zoster vaccination remain. So far, as long-term results on protection are not provided, zoster vaccination is recommended only once. Generally, immunogenicity in subjects aged 50 years or older has been demonstrated and safety was proven for healthy individuals, but efficacy drastically drops in the very old subjects. It is not defined whether the vaccine is safe in immunocompromised patients with pharmacological immunosuppression, whether the high-dosed attenuated VZV strain can be transmitted to other persons within the household of the vaccinee and whether it is beneficial in patients with recurrent episodes of herpes zoster.

Approaches to Enhance Immunogenicity of Vaccines

Most experiences with enhancing immunogenicity of vaccines exist for influenza by focusing on different application routes, adjuvants (cytokines, cationic liposomes, virosomes, MF59, Toll-like receptor ligands), increase in antigen dose and mechanisms to increase thymic function and T cell responses (table 2).

The use of higher doses of inactivated influenza vaccines containing four times more hemagglutinin than standard-dose vaccines has been shown to produce higher humoral immune responses in subjects aged ≥65 years with maintenance of favorable safety profile [40].

For the intradermal application route of inactivated influenza vaccines, a safe and immunogenic profile could be described with significant advantages in terms of higher acceptability by the patients, higher immunogenicity in the elderly and also dose sparing in adults younger than 60 years compared to the intramuscularly administered vaccine [41].

Another approach was shown in neonatal mice. It aimed to enhance the cell-mediated immune response by coadministration of the vaccine along with cytokines that promote Th1 responses, e.g. IL-12 [42]. In mice, an enhanced humoral and cellular Th1 response could also be reached after immunization with a trivalent influenza A (H1N1) vaccine with cationic liposomes as adjuvant [43] creating higher antigen-specific CD4+ T cell responses with a more than 30-fold dose-sparing effect [43].

A very long experience exists with adjuvants in seasonal influenza vaccination, such as MF59 [44, 45] and virosomes [46], increasing efficacy of influenza vaccination by inducing specific CD4+ T cell responses, strong and long-lasting memory T and B cell responses and by broadening the immune responses beyond the influenza strains included in the actual vaccine [44] with a favorable outcome also in small children [45].

The use of live attenuated influenza vaccines to enhance the immunological response in risk groups has been discussed for years. Although an intranasal, trivalent, cold-adapted, live attenuated intranasal influenza vaccine failed to induce cross-reactive protective immunity to other non-vaccine influenza subtypes and was not efficacious in elderly, it can be safely administered in children with high efficacy [47].

Discussion

The characteristics of the maturation of the adaptive immune system and its implications on the immune response to vaccines have been discussed in this review. Regarding preterm and term neonates, although early protection against vaccine-preventable infectious diseases is highly desirable, it has been demonstrated for most vaccines that only an incomplete immune response can be mounted with doubtful persistence of immune memory. This is very similar to vaccinations in the elderly, in whom less significant antibody concentrations or faster fading of specific antibody and cellular responses have been observed in many cases. However, in most cases protection from clinically relevant or severe disease can be provided also in small infants as well as in geriatric patients by early vaccination. However, several approaches to enhance immunogenicity of vaccines and to promote the persistence of the vaccine-specific immune response have to be undertaken considering the aspects of an immature immune system in neonates and small infants and of a terminally differentiated immune system in the elderly (table 2). At both age extremes, Th1 responses and sufficient cytotoxicity of lymphocytes have to be improved, e.g. by use of adjuvants [42, 44–46], by concomitant vaccination with other vaccines [22], by change in antigen concentrations, e.g. high-dose vaccines for influenza [40] or zoster [39] in the elderly, or implementation of other dose intervals [15, 20]. Although conjugation of proteins to polysaccharide antigens has been demonstrated to be highly efficient in small children to induce a significant immune response and memory [17], it has yet to be proven whether this approach is of similar benefit in elderly persons [35].

Many studies in neonates and geriatric persons teach us that antibody levels alone may not correlate with protection from symptomatic disease as it is still unclear how the local skin and mucosa barriers, the components of the innate immune system and the specific cellular response contribute to protect from pathogen intake, subclinical infection and relevant clinical disease. Thus, it also appears necessary to think of other end points than antibody concentrations to assess vaccine efficacy particularly in the elderly as also the cellular immune response may be impaired by the mechanisms of immunosenescence or due to underlying health conditions or immunosuppressive treatments for cancer, autoimmune disorders or chronic inflammatory conditions. Whereas most of the reasons for a low Th1 response in neonates and small infants are well understood [4–6], elderly persons have a high heterogeneity in their health states, and therefore a focus should be put on the exploration and restoration of the age-dependent immune dysregulation to improve immune functions. Thus, biomarkers of immunosenescence need to be defined which help to identify elderly persons in whom newly applied vaccines are likely to show low efficacy.

Several concepts to improve immunogenicity, efficacy and effectiveness under consideration of safety aspects have been also introduced particularly for the elderly. However, vaccination campaigns may be ineffective in protecting the elderly against complications from severe infectious disease, as not only socioeconomic aspects, such as the access to vaccinations, affect the success of immunization but also the age-related immunological impairment. Especially, nursing home patients not only show dysfunction of their innate and adaptive immune systems caused by physiological aging but also by secondary age-related effects, such as chronic inflammation, hormonal changes, frailty, functional status, malnutrition and psychosocial stress creating an immune risk profile influencing their vaccine response (table 2). Therefore, a concept of protection of unvaccinated, geriatric patients, but also of small infants and of neonates, is to improve herd protection particularly by vaccinating close contact persons (e.g. parents, siblings) and health care workers of those individuals. Additionally, in neonates, transplacental transmission of antibodies induced by maternal vaccination has to be considered for indirect protection from vaccine-preventable diseases [12].

Another difference between small infants and elderly people exists in the fact that children vaccinated in early childhood should maintain their protection against vaccine-preventable diseases throughout their whole life, which implies the need for vaccines inducing long-term immune memory. Thus, lifespan vaccine programs should be implemented to all individuals on a population level not only to improve herd protection and to maintain protective antibody levels and immune memory but also to cover all age groups, to protect unvaccinated elderly persons and to provide indirect protection for neonates and small infants.

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