REVIEW ARTICLES

Immunosenescence and vaccine failure in the elderly

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ABSTRACT. An age-related decline in immune responses in the elderly results in greater susceptibility to infection and reduced responses to vaccination. This decline in immune function affects both innate and adaptive immune systems. A meeting of experts in immunology and gerontology in Paris, France, in April 2008, considered current understanding of immunosenescence and its clinical consequences. Essential features of immunosenescence include: reduced natural killer cell cytotoxicity on a per cell basis; reduced number and function of dendritic cells in blood; decreased pools of naive T and B cells; and increases in the number of memory and effector T and B cells. In particular, an accumulation of late differentiated effector T cells, commonly associated with cytomegalovirus infection, contributes to a decline in the capacity of the adaptive immune system to respond to novel antigens. Consequently, vaccine responsiveness is compromised in the elderly, especially frail patients. Strategies to address the effects of immunosenescence include ensuring that seroprotective antibody levels against preventable infectious diseases are maintained throughout adulthood, and improving diet and exercise to address the effects of frailty. New vaccines are being developed, such as intradermal and high-dose vaccines for influenza, to improve the efficacy of immunization in the elderly. In the future, the development and use of markers of immunosenescence to identify patients who may have impaired responses to vaccination, as well as the use of end-points other than antibody titers to assess vaccine efficacy, may help to reduce morbidity and mortality due to infections in the elderly.

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INTRODUCTION

Immunosenescence may be defined as a constellation of age-related changes to the immune system, resulting in greater susceptibility to infection and reduced responses to vaccination.

In recent decades, the proportion of elderly people in the population has increased, and it has been predicted that people over 60 years of age will account for at least 20% of the population of Europe and the USA by 2050 (1). Immunosenescence is therefore an important consideration for healthcare providers, due to the burden that common infectious diseases (such as influenza and pneumonia) place on healthcare systems. Although vaccinations against certain infections are recommended in the elderly, their efficacy is reduced in this population compared with young adults (2).

To improve the health of the elderly population, we require greater understanding of the clinical manifestations and consequences of immunosenescence, as well as increased knowledge about potential markers of this decline in immune function. Greater appreciation of the influence of frailty on morbidity and mortality is also needed. By combining this knowledge, strategies to address immunosenescence can be developed. With this in mind, experts in the fields of immunology and gerontology convened at a meeting organized by Sanofi Pasteur MSD in Paris, France, on 28 April 2008, with the objectives of

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discussing the current understanding of immunosenescence and considering strategies to improve the efficacy of vaccines in the elderly. This paper provides a synthesis of the presentations and discussions at that meeting.

FEATURES OF THE AGING IMMUNE SYSTEM

Immunosenescence affects both innate and adaptive immune systems, and manifests as alterations in both numbers and functions of the various immune cell types (Table 1).

Age-related changes in the innate immune system

Phagocytosis of pathogens by neutrophils and macrophages is part of the first line of defence against infection. Although the number and phagocytic capacity of neutrophils are preserved in the elderly, other functions such as superoxide production, chemotaxis, signal transduction and apoptosis are reduced (3). The numbers of macrophage precursors and bone marrow macrophages are reduced in elderly humans, although the number of circulating monocytes does not decline with age (3). Macrophages also show age-related reductions in phagocytosis, chemotaxis, superoxide production, signal transduction, expression and function of Toll-like receptors, cytokine production, and induction of major histocompatibility class II antigens in response to interferon (IFN)-γ (3).

Natural killer (NK) cells play a significant role in the innate defence against virus-infected cells and tumours (4). Some studies have reported that the cytotoxicity of NK cells in the elderly population is preserved (5, 6), others that it is decreased (7, 8). This variability is probably partly due to differences in the health status of the individuals studied and the methods used to assess cytotoxicity (9). Nevertheless, there is evidence that NK-cell activity varies between elderly individuals, with consequences for health. For example, decreased NK-cell function is associated with an increased incidence of infectious diseases and death due to infection in elderly adults (8, 10, 11). Conversely, preserved NK-cell function is associated with better health status, a lower incidence of respiratory tract infections, and a better response to influenza vaccination (12). Furthermore, NK-cell cytotoxicity is generally well preserved in centenarians (13, 14). Despite this, there is evidence that NK

Table 1 - *Summary of age-related changes in human innate and adaptive immune systems.*

Innate immune system	**Adaptive immune system**
Proinflammatory cytokines Production leading to subclinical inflammatory status	T cells Thymic involution Decreased – naive (CD45RA+CD28+) CD8+ T cells – TCR repertoire – capacity to replicate – capacity to respond to novel antigens – effector memory CD4+ T cells Increased – memory (CD45RA–CD28+) CD8+ T cells – effector (CD45RA+CD28–) T cells – end-stage differentiated effector T cells – IL-4-producing CD8+ T cells – central memory CD4+ T cells
Neutrophils Unchanged – number – phagocytosis Decreased – superoxide production – chemotaxis – apoptosis – signal transduction	
Macrophages Unchanged – number Decreased – phagocytosis – superoxide production – chemotaxis – apoptosis – signal transduction – cytokine production	
Natural killer cells Decreased – signal transduction – response to cytokines – cytokine production – cytotoxic activity (conflicting results)	B cells Decreased – naive B cells – diversity of antibody responses – class switching and somatic recombination TCR repertoire Increased – effector B cells
DCs Unchanged – number of plasmacytoid DCs Decreased – total and myeloid DC numbers in peripheral blood – thymic DCs – number and migration of Langerhans' cells – IL-12 production by peripheral blood DCs	

DC: dendritic cell; IL: interleukin; TCR: T-cell receptor.

cells have an age-associated reduction in their ability to respond to cytokines such as interleukin (IL)-2, IL-12 and tumour necrosis factor (TNF)-α, resulting in impairment in their capacity to kill target cells and to synthesize chemokines and cytokines (9). Consequently, the ability of NK cells from elderly individuals to interact with the rest of the immune system is reduced.

Dendritic cells (DCs) are responsible for the capture and processing of antigens for presentation to T cells. The way in which DCs present the antigen also determines the nature of the immune response, and the quality and intensity of adaptive immune responses (15). Two principal types of DCs are recognized: myeloid (mDCs) and plasmacytoid (pDCs). The mDCs exist in an immature state within peripheral tissues (as in the skin, where they are present as Langerhans' cells and dermal DCs), but they become activated and mature when exposed to antigens, such as those associated with microbial pathogens and dying cells (16). In steady-state conditions, pDCs are present in peripheral tissues at a very low level, but they can be recruited into inflamed tissues (17). Activated mDCs produce mainly IL-12 (16), while pDCs produce IFN-α in response to viral infections and IL-4 in response to parasites (17).

Peripheral blood is the most accessible source of DCs for direct analysis or to obtain monocyte-derived DCs. Hence, the results of studies with DCs may depend on the methods used to isolate and purify the cells, and the culture conditions in which they are differentiated and/or maintained. Analysis of DCs from fresh blood by flow cytometric methods, which allow cell characterization directly in whole peripheral blood samples, has shown that there are significant reductions in the total number of DCs and of mDCs in healthy people over 60 years of age compared with younger individuals (18). In addition, peripheral blood DCs from elderly people have a more mature phenotype and a decreased capacity to produce IL-12 when stimulated. The number of CD34+ cells, which are DC precursors, declines progressively with age, whereas the number of monocytes, which can also act as DC precursors, increases with age. The number of pDCs does not appear to be affected by aging (18).

Currently, knowledge about the effects of aging on DCs from various tissues in humans is limited. The number of thymic DCs is markedly reduced in the elderly compared with younger individuals, and the expression of several surface antigens is also decreased (19). It is also known that Langerhans' cells are present in the epidermis in lower numbers in the elderly, and they show reduced migration out of the epidermis in response to TNF-α (20).

The age-associated changes in the activity of cells in the innate immune system also reduce the capacity for interactions between cells. For example, a decline in collaboration between NK cells and DCs may affect the function of DCs to prime T cells (21). Taken together, defects in the processing and presentation of antigens by the cells of the innate immune system contribute to diminished activation and stimulation of cells in the adaptive immune system.

Elevated plasma concentrations of interleukin-6 (IL-6), IL-1b, and tumor necrosis factor-alpha (TNF-α) have also been described in elderly populations. This progressive proinflammatory state in elderly persons has been called 'inflamm-aging' (22). This seems to contradict the functional defects observed in innate immune cells. However, it is believed that chronic subclinical inflammation is caused by chronic stimulation of the innate immune system by products of degradation processes and/or by the partial inability of the aged immune system to eliminate certain pathogens. This could lead to chronic, yet inefficient, innate immune responses.

Age-related changes in the adaptive immune system

<u>T cells</u>

The most extensively documented age-related changes in the adaptive immune system arise in the thymus. The volumes of the thymic cortex and medulla show a continuous involution from the first year of life until death (23), and only a small amount of tissue remains by 50 years of age. Consequently, the output of naive T cells is reduced, and the T cell pool in later life comprises mainly memory and effector T cells (2). Expression of the cell surface molecules CD45RA and CD28 is considered to be characteristic of naive T cells, and it has been found that the numbers of CD45RA+CD28+ CD8+ T cells are depleted in both the lymph nodes and circulation of people over 65 years of age compared with those under 30 (24). In addition, the CD45RA+CD28+ CD8+ T cells from elderly people display a restricted T-cell receptor (TCR) repertoire, and have shortened telomeres, indicating a reduced capacity to replicate and respond to novel antigens compared with young adults (25). Together, the reductions in the number and functional repertoire of naive T cells in the elderly contribute to an impaired response to primary vaccination.

There is also considerable variation between elderly individuals in the ratio of memory (CD45RA–CD28+) T cells to effector (CD45RA+CD28–) CD8+ T cells, and this appears to have significance for immune responsiveness. For example, healthy people over 60 who had a high percentage of CD45RA–CD28+ CD8+ T cells were found to have a reduced response to influenza vaccine compared with younger individuals (28-35 years of age), although they still achieved protective antibody responses. In contrast, elderly volunteers with a predominance of CD45RA+CD28– CD8+ T cells failed to respond to influenza vaccination (Fig. 1) (26). Furthermore, elderly individuals with a good response to vaccination had CD8+ memory T cells that also express CD25. These CD25+CD8+ T cells, which are neither activated nor regulatory, produce large amounts of IL-2 and some IL-4, but little IFN-γ. Conversely, individuals with a poor response

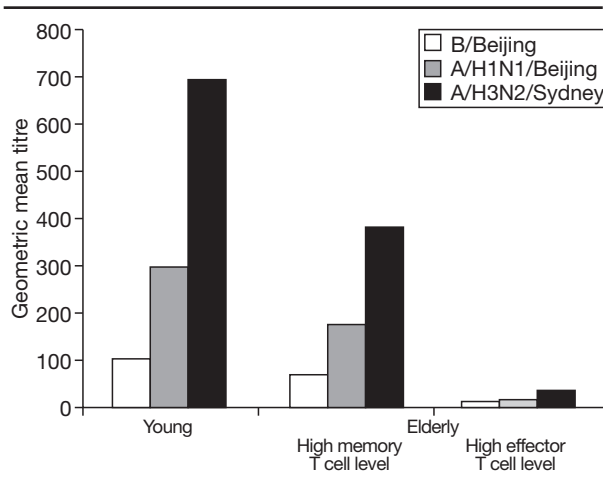

Fig. 1 - *Geometric mean anti-influenza haemagglutinin antibody titers 4 weeks after influenza vaccination in young adults (28-35 years) and healthy adults (60+) with a high proportion of either memory (CD45RA–CD28+) or effector (CD45RA+CD28–) CD8+ T cells. Post-vaccination antibody titers >1:40 are generally considered protective. Adapted from (26), Copyright 2002, The American Association of Immunologists, Inc.*

to influenza vaccination had CD25– CD28+CD8+ T cells, which produce little IL-2 and no IL-4 but do produce large amounts of IFN-γ. CD25+ CD8+ IL-4-producing T cells are not seen in healthy adults under 40, but they are present in 36% of people over 60 (27). Further analysis has revealed that the CD25+ CD8+ memory T cells have a more diverse TCR repertoire than CD25– CD8+ T cells, which suggests that accumulation of these cells in elderly people can maintain immune responsiveness in the absence of naive T cells (28). Recent studies using eight-colour cytofluorometric analysis have identified additional memory T-cell populations that changed with increasing age. Thus, memory T-cell subsets tended to be CD127+CD95– in young donors and CD127+CD95– in persons of advanced age (29).

As previously mentioned, the decline in the number of naive T cells in the elderly is accompanied by an accumulation of highly differentiated CD28– CD8+ effector T cells. These cells are absent at birth, but come to represent the majority of circulating CD8+ T cells in the elderly population (30). The characteristics of CD28– CD8+ effector T cells include short telomeres, a highly-restricted TCR repertoire, impaired capacity to migrate to lymph nodes, decreased ability to be stimulated by antigen-presenting cells, resistance to apoptosis, and production of large amounts of IFN-γ (2, 30).

Chronic infections, which provide repeated antigenic stimulation, are believed to contribute to the accumulation of CD28– CD8+ T cells. For example, cytomegalovirus (CMV) infection is associated with a decline in the naive T-cell pool and an increase in the number of CD28– CD8+ T cells in adults of all ages, but particularly in those over 65 years of age (31). A large proportion of the CD28– CD8+ T cells in elderly people seropositive for CMV are also CD45RA–, suggesting that they have reached the end-stage of replicative capacity (31). Typically, there is substantial clonal expansion of CMV-specific CD8+ T cells, which can eventually account for up to one-quarter of the total CD8+ T cell population in seropositive individuals (32); these cells frequently bear markers of late-stage differentiation (33). CMV infection is also associated with a significant reduction in the population of CD25+ CD8+ T cells that are responsible for good humoral immune responses in the elderly population (31). Together, these effects of chronic CMV infection on the T-cell population restrict the capacity of the adaptive immune system to respond to other antigens.

CMV seropositivity and an increased number of CD28– CD8+ T cells are two features of the immune risk profile (IRP), which has been shown to predict mortality in people over 85 years of age (34-36). Other features include a CD4+:CD8+ T-cell ratio <1 and poor T-cell proliferative responses to mitogens (37, 38). Longitudinal analysis of CD8+ T-cell clones suggests that CMV is one of the driving forces for acquiring an IRP (39). However, CMV-seropositive nonagenarians with an IRP had a significantly lower number of CD8+ T-cell clones compared with age-matched, non-IRP individuals, and this decrease in clone numbers was associated with a shorter survival time (39). This shrinkage in the T-cell repertoire of nonagenarians with an IRP is accompanied by low-grade inflammation, which contributes to frailty and is an independent predictor of death (40).

CD4+ naive T cells are less affected by aging than CD8+ T cells. Although their total number also decreases with age, it is not as low as naive CD8+ T-cell counts. However, studies in mice do demonstrate that naive CD4+ T cells from older animals are functionally impaired, displaying decreased responsiveness to TCR stimulation and altered profiles of cytokine secretion compared with naive CD4+ T cells from young animals (30, 41). In contrast, there is no evidence of functional impairment of memory CD4+ T cells with age (42). However, it has been reported that people over 65 have a higher number of central memory CD4+ T cells and a reduced number of effector memory CD4+ T cells compared with adults under 40 (43). An age-associated increase in CD4+ central memory T cells has been confirmed in several European populations (44). These changes in the composition of memory CD4+ T-cell subsets may contribute to impaired immune responses to viral infections and vaccines (30).

B cells

Age-related changes in B cells also contribute to the decline in the adaptive immune response in the elderly; re-

duced numbers of B cells are part of the IRP. There is a reduction in B-cell lymphopoiesis, which results in a decrease in the number of naive B cells, whereas effector B cells accumulate in old age (45). Consequently, there is a reduction in the diversity of antibody responses (46). In addition, the class switching and somatic recombination that are essential for antibody diversity and the production of high-affinity immunoglobulin G antibodies are impaired in elderly individuals (47), resulting in weak and low-affinity antibody responses. In addition, changes in CD4+ T helper cell function contribute to impaired activation of B cells in the elderly (48).

In summary, aging produces comparable changes in T and B cell populations in the elderly, including reductions in the numbers of naïve cells and increases in the numbers of effector and memory cells. The resulting reductions in the repertoire of immune functions and defects in cooperation between T and B cells contribute to the impaired immune responses seen in the elderly.

CLINICAL CONSEQUENCES OF IMMUNOSENESCENCE

The age-related changes in the innate and adaptive immune system may have clinical consequences at different levels. An age-related decrease in cellular function within the innate immune system may impair the elimination of pathogens. This can lead to chronic activation of innate immunity, trigger inflammatory processes and thus contribute to the generation and progression of age-associated diseases, such as osteoporosis or atherosclerosis (2). This subclinical inflammation may also be an important contributor to the progression of sarcopenia, the degenerative loss of skeletal muscle that occurs naturally with age (49). Thus, immunosenescence may indirectly affect many different organs.

The decline in the repertoire of both innate and adaptive immune responses in the elderly results in increased susceptibility to infections and a greater risk of mortality due to these infections compared with younger people (50). Mortality rates for conditions such as cancer and cardiovascular disease also appear to reach a plateau around 80 years of age, whereas the rates for pneumonia, influenza, bronchitis and gastroenteritis continue to increase (51).

The age-related decline in the adaptive immune system is also apparent in the decrease in post-vaccination antibody concentrations over time in the elderly population. For example, antitetanus antibody concentrations below the fully protective level were reported in 16% of people over 60 years of age who had been vaccinated in the previous 1-5 years, and in 20% of people over 60 who had been vaccinated 6-10 years previously. In contrast, tetanus antibody concentrations below protective levels were very rare (≤3%) in people under 60 (52). Studies of influenza vaccine in the elderly have also reported a rapid decline in antibody responses, with a reduction in seroprotection rates between 1 and 5 months post-vaccination (53). Maintenance of seroprotective levels of antibody is important, because they have been shown to be predictors of both protection against infection (54) and response to booster vaccination in the elderly (55).

Vaccination against influenza, pneumococcal pneumonia and herpes zoster can help to reduce the risk of infectious diseases in the elderly population. However, these vaccines are less effective in the elderly compared with young adults (2). For example, at least 25% of healthy elderly people do not develop antibody titers considered protective against influenza 1 month after vaccination (56, 57). A quantitative review of 31 vaccine antibody response studies found that seroconversion and seroprotection rates for all three antigens included in the trivalent influenza vaccine were significantly higher in younger volunteers (age 17-59 years) than in elderly individuals (age 58-104 years) (Table 2) (58). Multivariate step-wise regression showed that the responses for all three antigens and both outcomes were 2-4-fold higher among younger adults than in the elderly. Furthermore, within the elderly population, people aged 75 years or older had significantly lower responses in terms of seroconversion for all three antigens and seroprotection for the H1 and H3 antigens compared with people under 75 (Table 2) (58). However, the seroprotection rate for the B antigen was higher in those over 75.

However, it is important to recall the heterogeneity of the elderly population in terms of overall health and functional capacity. In recent years, there has been growing recognition of a 'frailty phenotype' in the aging population, which is manifested in unintentional weight loss, exhaustion, weakness, slow walking speed and low physical activity, and is associated with the risk of institutionalization and mortality (59, 60) and of impaired immune responses after influenza vaccination (61, 62). In this respect, frailty has been defined as: "a stage of age-related physiologic vulnerability resulting from impaired homeostatic reserve and reduced capacity of the organism to withstand any stress" (63). Interestingly, the only biomarkers for frailty established to date are markers of increased coagulation (e.g., fibrinogen, factor VIII) and inflammation (e.g., C-reactive protein, IL-6) (64-67). Chronic inflammation can impair the functions of the innate immune system (2), and elevated levels of IL-6 are also associated by the IRP with mortality in nonagenarians (40).

STRATEGIES TO ADDRESS IMMUNOSENESCENCE

A range of potential strategies may be used to address the decline in immune function in the elderly (68, 69). For example, greater importance could be placed on the maintenance of seroprotective antibody levels against infections such as diphtheria, tetanus and pertussis

Table 2 - *Post-vaccine responses (unadjusted) in young (17-59 years)* vs *elderly (58-104 years) people, and in elderly people under 75* vs *elderly people ≥75 years across 31 studies, by influenza subtype.*

Vaccine component	Age group	Seroconversion (% of individuals with four-fold antibody increase)			Seroprotection (% of individuals with antibody titers >40)		
		n	% positive	Unadjusted OR (95% CI)	n	% positive	Unadjusted OR (95% CI)
H1N1	Young	913	60	Reference	1151	83	Reference
	Elderly	4492	42	0.48** (0.41-0.55)	4643	69	0.47** (0.40-0.55)
H3N2	Young	913	62	Reference	1151	84	Reference
	Elderly	4492	51	0.63** (0.55-0.73)	4643	74	0.53** (0.45-0.63)
B	Young	913	58	Reference	1151	78	Reference
	Elderly	4492	35	0.38** (0.33-0.44)	4643	67	0.58** (0.50-0.67)
H1N1	<75 years	1945	55	Reference	1883	75	Reference
	≥75 years	2492	32	0.38** (0.34-0.43)	2706	65	0.63** (0.58-0.70)
H3N2	<75 years	1945	58	Reference	1883	83	Reference
	≥75 years	2492	46	0.63** (0.56-0.71)	2706	68	0.45** (0.40-0.50)
B	<75 years	1945	41	Reference	1883	62	Reference
	≥75 years	2492	29	0.58** (0.51-0.66)	2706	71	1.47** (1.34-1.60)

CI: confidence interval; OR: odds ratio. **$p<0.001$.
Adapted from (58), with permission from Elsevier.

throughout adult life by giving more booster vaccinations, if necessary. A correlation between pre- and post-vaccination antibody levels has been reported for these three diseases in elderly adults following boosters (Fig. 2) (55), and this may mean that some recipients fail to achieve seroprotective levels even after boosters.

The uptake of vaccines in the elderly population also needs to be improved. The benefits of childhood vaccines are generally well accepted by both healthcare providers and parents, and preventive medicine strategies should aim to achieve a similar status for vaccines for aging adults. To increase the likelihood of a good immunological response, it may also be appropriate to give primary doses of herpes zoster and pneumococcal vaccines as early as possible.

Interventions to address some of the features of frailty may also have beneficial effects on immune function-

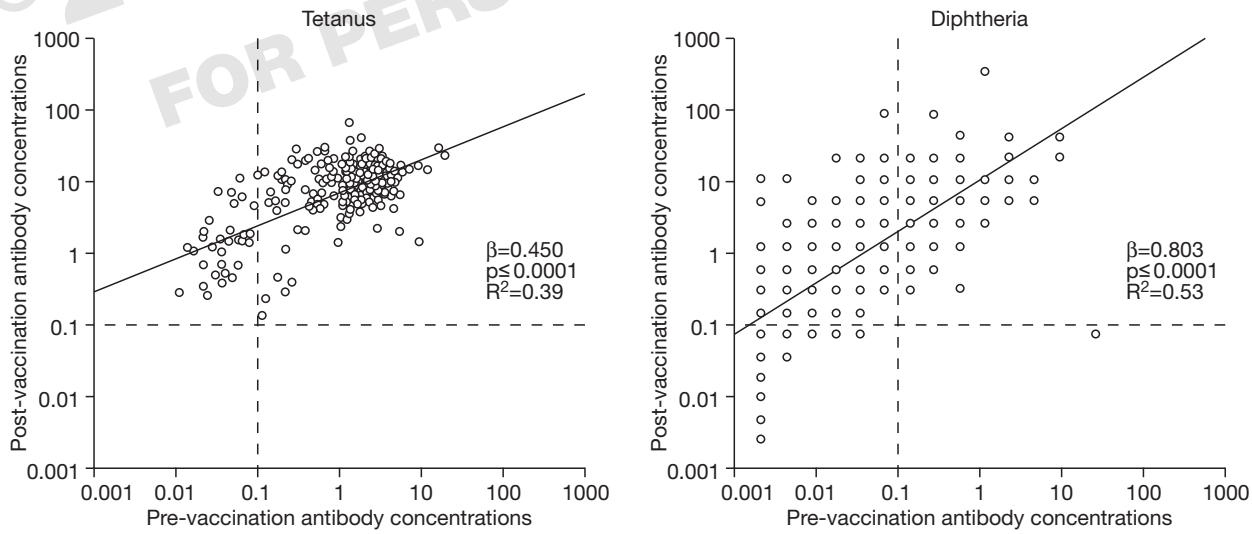

Fig. 2 - *Correlation between pre- and post-vaccination antibody concentrations (logarithmic scale) for tetanus and diphtheria in healthy elderly people aged 59-91 years. Dashed lines: antibody concentrations required for full protection. Individuals with values in lower left of plot were unprotected before and after vaccination. Adapted from (55), with permission from Elsevier.*

ing, by improving overall functioning in the elderly. Exercise training has been shown to reduce the decline in physical function (70) or even improve physical performance (64) in frail, elderly people. Elderly adults who exercise regularly have enhanced immune responses after influenza vaccination compared with sedentary individuals (71). Poor nutrition is associated with the development of frailty (59). Improving the nutritional status of elderly people may therefore help to improve their immune functioning (72-74). It is interesting to note that a study of nursing-home residents and their carers found that higher responses to vaccination were associated with younger age and also with high serum concentrations of total proteins, albumin, folate and vitamin E. After adjusting for age and gender, the association between serum vitamin E concentration and immune response remained significant (75). Lastly, psychosocial factors have been found to modulate immunity to influenza vaccination in elderly volunteers (71, 76-79).

New vaccines are currently being developed in an attempt to improve the efficacy of immunization in the elderly population. For example, strategies under consideration for influenza vaccination include the use of higher doses (60 *vs* 15 μg) of the three antigens (80), intradermal delivery (81), or the use of existing potentiated vaccines, such as virosomal or MF-59 adjuvanted vaccines (82). High-dose and intradermal vaccines are both reported to induce greater antibody responses in elderly volunteers compared with the standard intramuscular vaccination with 15 μg of each antigen (80, 81).

Lastly, vaccine trials should be designed to reflect the variations in immune function and health status across the elderly population. For example, greater understanding of the effects of advanced age and of frailty of the response to vaccination is required. These physiological factors may have a substantial influence as confounding effects in clinical trials. The use of end-points other than antibody titers and seroprotection rates should also be considered for vaccine studies in elderly people. For example, it has been reported that the frequency of CD28– CD8+ (26, 83) or CD25+ CD8+ (28) T cells, or measures of post-vaccination T-cell responses, such as the IFN-γ:IL-10 ratio and granzyme B production (84), may be better at predicting induction of protective immune responses after influenza vaccination than antibody titers in the elderly population.

CONCLUSIONS

Immunosenescence, a reduction in immune responses affecting both innate and adaptive immune systems, is part of the overall decline in physiological functioning that is seen as a result of aging. This process of immunosenescence contributes to morbidity in elderly people through increased susceptibility to infections and reduced effectiveness of vaccinations. Better understanding of age-associated changes in the immune system and of factors contributing to frailty should enable the development of more effective vaccines and vaccination strategies to protect the elderly against infections. For example, the use of potential 'markers' for immunosenescence (e.g., changes in the composition of T and B cell populations, altered NK-cell activity, reduced numbers of peripheral blood DCs or changes in cellular interactions) may help to identify those who are likely to show a reduced response to vaccination. Similarly, measurements of inflammatory markers, such as IL-6, may identify patients at risk of developing the frailty phenotype and/or reduced immune functioning (85). These patients could potentially benefit from other interventions, such as dietary management, to improve their overall functioning and immune responses. Lastly, new approaches to vaccination in the elderly, such as intradermal delivery or higher doses, offer promise of improved protection against infections in the future.

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