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Vaccination in the elderly: an immunological perspective

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Abstract

Successful vaccination of the elderly against important infectious pathogens which cause high morbidity and mortality represents a growing public health priority. Building upon the theme of aging and immunosenescence, we review mechanisms of human immunosenescence and the immune response to currently-licensed vaccines. We discuss the difficulties in identifying the risk factors that, in addition to aging, cause immunosenescence and address the relative paucity of vaccine studies in the elderly. We conclude that vaccine responses are blunted in the elderly when compared to that of healthy young adults. However, it is also clear that our understanding of the mechanisms underlying immunosenescence is limited and much remains to be learned in order to improve the effectiveness of next generation vaccines.

Introduction

The population of persons older than 65 years is expected to rise dramatically in most areas of the world because of advances in average life expectancy. Worldwide, the number of elderly persons is expected to increase from 600 million currently to nearly 2 billion in 2050 and, in developed countries, 25% of the population will be older than 65. At the same time, as individuals age, immunosenescence causes an increased susceptibility to infections, which results in greater morbidity and mortality compared to younger adults. Demands on health services will clearly escalate as a result of this demographic revolution. In response, successful vaccination against important infectious pathogens of the elderly represents a major preventive strategy that must be emphasized now and in the future. Unfortunately, immunosenescence not only impairs the ability to fend off infection but also the capacity to respond to vaccination. In this article, we will provide a general discussion on how immunosenescence affects the quantity and quality of the human response to immunization. We will review currently approved vaccines with a focus on recommendations for their use in the elderly and discuss current data on vaccine immunogenicity, protective efficacy and immunological correlates of protection. We will also briefly discuss some of the lessons we have learned and what still remains unknown regarding the effects of aging on the human immune response.

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Mechanisms leading to immunosenescence

There is still an ongoing debate among immunologists and vaccine specialists regarding the optimal vaccine strategy for the elderly. Whereas neutralizing, opsonizing, hemagglutinating, etc. antibodies have been the traditional gold standards for evaluating vaccine efficacy, it is becoming increasingly clear that for many pathogens, robust cell-mediated immunity (CMI) is required for protection. A second challenge toward vaccine development is the heterogeneous nature of the target population including age, history of previous infection, and immune system function. It is clear that what constitutes a successful vaccine in infants and young children may differ dramatically from the features required to protect the elderly. For example, although influenza immunization of young adults provides 65–80% protection against illness caused by a virus present in the vaccine, vaccination of the elderly only affords 30–50% protection against disease [1]. Elderly persons who fail to mount antibody or CMI responses to the vaccine are at highest risk, but even those who do respond to vaccination show a reduced antibody titer and CMI compared to young individuals.

Given the broad range of responses and degree of protection afforded the elderly by prophylactic vaccines, there have been numerous attempts to identify immune system correlates of successful or unsuccessful vaccination. One prime example, demonstrated in three recent independent studies, indicates that poor responsiveness to influenza vaccination is significantly associated with the presence of high proportions of a population of $CD8^+$ T lymphocytes that lack expression of the co-stimulatory molecule CD28 [2,3,4] (also see the article by Weng et al. in this issue). Moroever, associations have been described between high proportions of $CD8^+CD28^-$ cells and the prevention of allograft rejection [5], accelerated progression of HIV-1 infection [6], head and neck tumors [7], cervical cancer [8], ankylosing spondylitis [9], and other diseases involving an inflammatory state; suggesting a generalized suppressor function. Of note, this same biomarker is part of a cluster of immune parameters, the so-called ‘immune risk phenotype’, that are associated with early mortality in longitudinal studies of the elderly [10].

The common theme in many of these reported accumulations of $CD8^+CD28^-$ T lymphocytes is chronic antigenic stimulation, be it by virus, alloantigen, autoantigen or tumor-associated antigen, which stimulates extensive cell division, ultimately leading to an end-stage of irreversible cell cycle arrest known as replicative senescence. Cell culture modelling of this process has identified a variety of characteristics associated with $CD8^+$T lymphocyte replicative senescence [11,12]. These senescent $CD8^+$ T cells are unable to enter the cell cycle and are resistant to apoptosis [13], leading to their progressive expansion over time *in vivo* [14] which coincides with a loss of CD28 expression [15] and the ability to upregulate telomerase [16].

The importance of sustained telomerase activity in the functional changes associated with T cell replicative senescence is underscored by experiments in which the catalytic component of human telomerase, hTERT, is transduced into virus-specific $CD8^+$ T cells from HIV-infected persons. In addition to enhanced proliferative potential and telomere length maintenance, HIV-specific production of interferon-gamma and cytotoxicity was significantly increased [17]. Similar results were obtained using a small molecule telomerase activator, suggesting that telomerase may have important immune-enhancing functions in addition to its specific effects on telomeres [17].

Cell culture kinetic studies on telomerase suggest that the more rapid loss of telomerase inducibility and CD28 expression in chronically stimulated $CD8^+$ versus $CD4^+$ T lymphocytes may provide a possible explanation for the observed preponderance of $CD28^-$

T lymphocytes within the $CD8^+$ subset during aging. Indeed, in many elderly persons, more than 50% of the peripheral $CD8^+$ T lymphocyte pool consists of $CD28^-$ cells, as compared with <20% of these cells within the $CD4^+$ subset [18]. At least within the $CD8^+$ T cell subset, one of the driving forces responsible for generating the high proportion of cells with memory, end stage phenotype seems to be herpesviruses, which establish latent infections early in life and persist for many decades, requiring continuous immunosurveillance [19].

There may be an indirect effect on vaccines caused by changes in the overall composition of the total T lymphocyte pool. $CD8^+CD28^-$ T lymphocytes are often part of oligoclonal expansions that crowd the immunological space [20,21], a feature that is associated with narrowing of the available T cell repertoire [22]. The poor response of elderly persons to neoantigens, including vaccine antigens, might be one manifestation of this more restricted repertoire. Thus, the cost of maintaining immune control over latent infections is that, by old age, there is a reconfiguration of the immune system, leading to reduced responses to vaccines aimed at preventing acute infections, particularly those never experienced before. One point that should be emphasized is that although priming to neoantigens is defective in the elderly, the recall to booster doses of an antigen in a previously primed elderly person seems to remain intact. Antigen specific memory $CD4^+$ or $CD8^+$ T cells, if elicited when young, persist into old age and can mediate effective CMI responses [23]. Therefore, aging appears to differentially affect T cell function at the naïve versus memory stages.

Recent evidence also supports the effect of aging on innate immunity, the first line of host defense (see the article by Kovacs and Shaw in this issue). These data underscore the wide-range of immune deficiencies which might play a role in decreased immune competence associated with aging.

SENIEUR Protocol for the study of immune responses in the elderly

Whereas controlling the entire immunological experience from birth to old age is possible in animal studies, clinical confirmation of the effects of immunosenescence and the conduct of vaccine immunological studies in human elderly individuals is difficult, due in large part to the extremely heterogeneous nature of the elderly population. These variables include: underlying medical conditions, use of medications, the history of previous infections, and exposure to various unaccountable environmental factors. These multiple confounding parameters may have a significant cumulative effect on immunity, independent of immunesenescence. Thus, the question becomes, how can these confounding factors be separated from phenomena directly associated with immunosenescence?

The most common method is to limit the study population to individuals with few or none of these confounding factors. Because the selection of study participants can be subjective and in order to clarify the effect of aging *per se* on immune function, strict volunteer selection criteria are mandatory. Toward this end, the SENIEUR Protocol was developed in 1984 by the working party of the EURAGE concerted Action Programme on Ageing of the European Community [24,25]. In order to minimize conflicting results between studies, the Protocol provides strict admission criteria for immunogerontological studies (TABLE 1). Volunteers recruited using the SENIEUR Protocol tend to have more homogeneous immune responses than those not satisfying the protocol. For example, among elderly that satisfy the SENIEUR Protocol, IL-2 synthesis and T cell responsiveness to cytokines and exogenous IL-2 were not much different from those observed in younger adult controls, suggesting that reduced IL-2 production is not associated with healthy aging [26]. Examples of exclusion criteria based on nutritional, metabolic, pharmacologic, demographic, and epidemiological factors will be discussed later in the section on hepatitis B vaccines. Aside from minimizing the influence

of measurable external factors on the immune system, a further advantage of the SENIEUR Protocol has been its validation by clinical experience [25].

However, there are several disadvantages of the SENIEUR Protocol. It requires a time-consuming, labor-intensive admission workup by highly skilled clinical research staff. Because only 10% −12% of ambulatory, reasonably healthy elderly persons actually satisfy the strict SENIEUR admission criteria [24], these individuals do not accurately reflect the target high-risk population. The difficulty in identifying and enrolling elderly participants who do satisfy the SENIEUR Protocol may explain why only a few vaccination trials have been conducted under its strict guidelines, i.e., Haemocyanin [27], tetanus [28,29], and influenza [30,31,32] vaccines. The remainder of elderly clinical vaccine trials have opted to use looser eligibility criteria, making the specific effect of immunesenescence difficult to dissociate from potential confounding and biasing factors that are independent of age [23]. With these caveats in mind, we will now review some of the prevailing data on the effect of age on the immunogenicity and efficacy of specific vaccines.

Pneumococcal vaccine

Infections caused by *Streptococcus pneumoniae* account for 25–35% of bacterial pneumonias resulting in hospitalization and thus remain a significant cause of morbidity and mortality in the elderly [33]. The current pneumococcal polysaccharide vaccine (PPV) was licensed in 1983 and is recommended for all individuals ≥ 65 years of age and those 18–64 years of age at risk for pneumococcal infection. This vaccine incorporates 23 pneumococcal serotypes including the six (6B, 9V, 14, 19A, 19F, and 23F) most frequently causing invasive drug-resistant infection in the United States. The current recommendation is for PPV to be administered once to anyone ≥ 65 years of age; and only once more if they had received PPV at age < 65 years and if it has been ≥ 5 years since that first dose.

While the efficacy of PPV was convincingly demonstrated in the 1970's by randomized, controlled trials in younger adults, the data for efficacy in elderly adults is not as persuasive. One problem with attempts to compare the efficacy of PPV in the elderly has been the dissimilarity of the study populations; in some studies frail elderly subjects with significant comorbidities are included, while in others only healthy elderly are studied, but none used the SENIEUR Protocol [34]. Another important variable among these clinical studies is the definition of the outcome variable of interest, e.g., lower respiratory tract infection, pneumonia-related death, or all-cause mortality. A further set of confounding factors relates to different criteria used to define pneumococcal disease, i.e., pneumonia defined by clinical symptoms alone, clinical symptoms with radiographic confirmation and confirmation using different culture and detection methods of various body samples, each having a different sensitivity and specificity for *S. pneumoniae*. Despite this variability, the cumulative data indicates a decreased PPV efficacy in immunocompromised hosts and waning vaccine efficacy with increasing age [35].

Although PPV afforded protection against blood culture proven invasive pneumococcal disease, prospective randomized controlled trials [36,37], large cohort studies [38], and numerous meta-analyses [39] have failed to reveal a protective effect in the elderly against non-bacteremic pneumococcal pneumonia. On the whole, these data support the use of PPV in the elderly to prevent bacteremic pneumonia, but also highlights the need for further vaccine research to prevent non-bacteremic pneumococcal disease.

The current and most accepted immunological correlate of protection of pneumococcal vaccines is based on the elicitation of antibodies against serotype-specific pneumococcal capsular polysaccharide, which facilitates opsonophagocytosis (Textbox 1). A greater than 2-fold increase in serotype-specific opsonophagocytosis assay (OPA) antibody usually

develops within 2–3 weeks in healthy adults, but the OPA antibody level that correlates with protection has not been clearly defined. Although PPV responses may not be consistent among all 23 vaccine serotypes, antibody levels are lower in the elderly and in those with chronic disease [33,41]. One the other hand, healthy elderly adults ≥ 75 years of age (modified SENIEUR protocol), when compared to adults ≤ 35 years of age, are able to elicit similar serotype-specific antibodies and antibody avidity following PPV vaccination [34]. The antibody response induced by PPV, because it is a polysaccharide and lacks a protein carrier, is a T lymphocyte-independent response, lacking immunological memory and the ability to mount a booster effect. As a result, revaccination after a second dose of PPV in persons ≥ 65 years of age is not recommended since the data for safety and immunogenicity is not conclusive. In contrast, polysaccharide conjugate vaccines (PCV, only licensed for pediatric use), which elicit T lymphocyte-dependent responses, results in increased immunogenicity, memory, and a booster effect in infants [42]. The single study, to our knowledge, which evaluated the immunogenicity of PCV versus PPV in vaccine-naïve elderly, found that a 7-valent PCV was more immunogenic than PPV and elicited a booster response to a subsequent vaccination one year later [43].

In conclusion, further research is necessary for the development of more effective means to prevent non-bacteremic pneumococcal pneumonia, especially for the elderly. Perhaps newer polysaccharide conjugate or protein-based (non-polysaccharide) pneumococcal vaccines will demonstrate stronger evidence of protection in the elderly.

Influenza Vaccine

Influenza virus infections account for up to 430,000 hospitalizations and 20,000–40,000 deaths annually in the U.S., among which >90% of the mortality occurs in the elderly population. These figures underscore the urgent need for more effective methods of primary prevention of influenza infection. The current influenza vaccines approved for use in the elderly consist of trivalent inactivated subvirions; purified viral components, containing 15 μg of hemagglutinin from the 3 representative virus strains that are believed to be the major circulating strains for the particular influenza season (currently types H1N1, H3N2, and B), are obtained from viruses grown from pathogen-free embryonated chicken eggs. Annual vaccination is recommended during the fall and early winter for all persons ≥ 50 years of age.

Although data on influenza vaccine effectiveness in the elderly is somewhat controversial, several estimates suggest that vaccination reduces influenza-specific hospitalization by 27–45% and death by 43–50% [1,44,45,46,47]. By contrast the efficacy, prevention of laboratory-confirmed influenza, of the same influenza vaccines among young adults is 70–90% [48]. There are few randomized controlled trials which include the elderly and the existing observational studies have been criticized for methodological problems including inadequate consideration of potential bias; frailty among the heterogeneous elderly population; variability in the serological match between the vaccine virus strains and the circulating influenza strains; and the use of outcome measures with low sensitivity (influenza-like illness rather than laboratory confirmed influenza). These methodological issues inherent in cohort studies have led to overestimates of efficacy [49] and also suggest that vaccination might not be reducing influenza-related mortality in the elderly[50,51].

The most accepted immunological correlate of protection is based on hemagglutination inhibition (HAI) antibody (Textbox 2). Reviews of the humoral immune response to influenza vaccines in the elderly have yielded conflicting results [53], yet an impairment in HAI responses is believed to occur [54]. The large variation in humoral immunity induced by influenza vaccines may be further complicated by so-called “original antigenic sin”,

which refers to the specific hemagglutinin and neuraminidase subtypes encountered during primary influenza infection, which is thought to affect all subsequent immune responses to the virus, particularly in old age [55]. Elderly persons who meet the SENIEUR Protocol criteria had diminished responses to H1N1 but not H3N2 virus compared to young adults [56], however following annually repeated vaccination there was no difference between age groups [31]. Since the priming histories to H3N2 were similar in the two age groups, it was suggested that priming (previous exposures) from similar virus strains might lead to increased heterotypic responses; viruses that closely resemble each other result in a booster effect rather than being recognized as new antigen and without booster effect.

Theoretically, the decrease in quantity of antibody, as measured by HAI, might be counterbalanced by an increase in antibody avidity as a result of subsequent vaccinations with the same antigen. However, over three consecutive seasons, elderly subjects failed to demonstrated a statistically significant increase in antibody avidity [57]. It has been suggested that the humoral response to influenza vaccine declines more rapidly in the elderly, but this postulate has also been questioned [58]. Therefore, the effect of immunosenescence on the ability of the humoral immune response to influenza vaccine to protect elderly individuals remains unclear.

Protection from influenza infections and the elicitation of humoral immunity requires an intact CMI response to vaccination. It is likely that vaccine efficacy is a result of a complex and carefully orchestrated interplay of multiple factors within the immune system and no single marker sufficiently predicts vaccine responsiveness. Although T cell responses may not completely protect from infection, antigen-specific T cell proliferative responses and the associated IL-2 and IFN-γ production is impaired [59,60] and protection is inversely associated with a shift from Th1 cytokines (e.g., IFN-γ) toward Th2 cytokines (e.g., IL-10) dominance [61]. Elderly with lower levels of IL-6 at the time of vaccination responded better to initial vaccination [32]; perhaps reflecting a state of chronic inflammation, termed inflammaging [62]. Lower granzyme B, a key effector mechanism of influenza-specific cytotoxic T cells (CTL)-mediated killing, was associated with laboratory confirmed influenza [63]. Cytotoxic NK cell activity has also been found to be associated with protection from all-cause respiratory tract disease and good HAI response to influenza [64].

In conclusion, there is an urgent need to develop a newer generation influenza vaccines to specifically address the limitations of the current vaccines in protecting elderly persons. One strategy to further protect the elderly is to focus on the vaccination of young children, a common pathway of respiratory virus transmission to the elderly. Although the currently available influenza vaccines do not optimally protect the elderly as a group, annual vaccination remains of outmost importance for public health and for individuals who may indeed benefit from vaccination.

Tetanus, diphtheria, pertussis, and tick-borne encephalitis vaccines

Whereas influenza and pneumococcal disease are the most frequently encountered infectious diseases in the elderly, attention should also be paid to the prevention of less frequent diseases such as tetanus, diphtheria, pertussis or even tick-borne encephalitis (TBE). Although tetanus infections have diminished dramatically since the tetanus toxoid vaccine was introduced, the disease has not disappeared; in 2005 there were 27 tetanus cases in the U.S. and 98 cases in the European Union. (http://ec.europa.eu/health/ph_information/dissemination/echi/docs/tetanus_en.pdf). The elderly represent the main risk group, both in terms of contracting the diseases as well as dying from serious complications [65]. A resurgence of diphtheria spread throughout the Russian Federation in the early 1990's [66]. In Canada, pertussis accounted for 16.2% of prolonged cough (1 to 8 weeks) in those >60

years old [67]. Adults have higher rates of complications than adolescents, including pneumonia [68]. Immunity to vaccination against *Bordotella pertussis* wanes after 5 to 10 years and rarely lasts more than 12 years [69]. New acellular vaccines have been tested in persons aged 19–64 years [70] but their immunogenicity and protective efficacy in persons > 65 years remain unknown.

Available combination vaccines for adult contain either low-dose diphtheria toxoid with tetanus toxoid or both compounds in combination with pertussis toxoid with or without inactivated polio-virus types 1/2/3. These vaccines are relatively inexpensive and readily available in developed countries. They should be given at ten year intervals throughout life. TBE vaccines contain inactivated virus and are recommend in areas where the disease is endemic. TBE endemic areas traverse Europe and include 27 European states.

Only a few studies have documented the number of persons immunized as well as the efficacy of tetanus, diphtheria and TBE vaccine in elderly persons [71,72,65,73,74,75,29]. These studies demonstrate that vaccination coverage is low and failure to have protective antibody concentrations are frequent. Interestingly, the results were similar for both SENIEUR compatible cohorts and patients in long-term care facilities [72,29]. The protective antibody titer against tetanus and TBE is dependent on both the time point of the last vaccination and age; persons over 60 years of age frequent do not have protective antibody [74]. There are only a few reports on CMI immunity against tetanus in elderly persons [76,29]. The success of booster vaccinations against tetanus, diphtheria and TBE also greatly depends on pre-vaccination antibody concentrations; greater pre-vaccination antibody levels were associated with better vaccine responses [75], suggesting that long-lived plasma cells and memory B cells might also play an important role in the maintenance of protective immunity.

Hepatitis B Vaccine

Safe and effective Hepatitis B virus (HBV) vaccines have been commercially available since 1981. Depending on the country, licensed HBV vaccines currently available include plasma-derived vaccines, prepared by harvesting particles of hepatitis B surface antigen (HBsAg) protein from the plasma of infected patients, and recombinant DNA vaccines produced in yeast or mammalian cells to generate the HBsAg. There is a decline in frequency of anti-HBs responses and a decrease in magnitude of anti-HBs titers with each decade of life over the age of 40 years [77,78]. Even when adjusting for risk factors associated with poor immune response, increasing age is an independent risk for inadequate HBs antibody responses [79]. In terms of seroconversion to HBsAg, a small study of “healthy geriatric patients” showed that 69% of 61–70 year olds (n=13), 44% of 71–80 year olds (n=16), and only 39% of 81–96 year olds (n=41) seroconverted after three vaccine doses injected at one-month intervals [77]. These low seroconversion rates contrast with the 96% seroconversion rates in younger adult populations with the same vaccine. In two meta-analyses, there was an increased risk of non-response to hepatitis B vaccine among healthy older individuals [80] and those with end stage renal disease on dialysis [81], respectively. A combined effect of dysregulation of the B and T cell compartments has been suggested as the cause of the decreased anti-HBs antibody response [82].

In addition to age, several host attributes are epidemiologically associated with diminished responses to HBV vaccines. These factors may co-exist in persons of all ages, including elderly persons, and confound the effects that are the direct result of immunosenescence. One of these attributes, somewhat theoretical, is that immunological tolerance or immunosuppression is induced by latent Hepatitis B virus infection (reviewed in [83]). A more recent hypothesis is that cytomegalovirus (CMV), which establishes persistent life-

long infection, drives clonal expansion and alters the phenotype and function of CD8 cells; such cellular alterations in turn might account for the senescent response to infections and vaccines [84,85,86]. A listing of factors other than age that might contribute to diminished immunity to hepatitis vaccination in the have been included in Textbox 3.

Currently, all hepatitis B vaccines licensed for human use in the USA have been formulated with aluminum salts, which are relatively weak adjuvants [97]. An increasing array of newer adjuvants are in phase 1 – 3 trials to improve HBV vaccines [98]. It remains to be proven if new adjuvant formulations can induce vigorous HBsAg antibody and CMI in elderly individuals similar to that induced in healthy 18–40 year old adults [99].

Shingles Vaccine

The shingles vaccine represents the rare success story of a targeted vaccine for the elderly that has proven to be highly effective. The article by Pawlec, Goronzy, and Akbar in this issue covers the story of shingles vaccine. We will only editorialize by stating that because the shingles vaccine does not depend principally on the declining naïve T cell population for priming immunity but rather on a memory cell (booster) response, it would be expected that immunesenescence plays a lesser role in the response to this vaccine in the elderly. However, age still matters, as illustrated by the decreasing efficacy seen in ≥ 80 year olds.

Other vaccines

Commercially available vaccines for other infectious pathogens exist, including meningococcal, polio, measles, mumps, rubella, polio, hepatitis A, yellow fever, and rabies. However, the burden of these particular diseases in the elderly residing in the developed world is very low and, therefore, routine vaccination of the elderly is not generally recommended. However these vaccines are offered to elderly travelers to high-risk regions. The meningococcal [100], rabies[101], and hepatitis A [102] vaccines are all less immunogenic in the elderly. There is no published information on the immunogenicity of the other vaccines listed or on the protective efficacy of any of them in the elderly. It is important to mention that vaccination with the live-attenuated 17-D yellow fever virus vaccine can rarely result in serious or fatal viscerotropic or neurotropic disease resulting from overwhelming systemic infection by the 17-D vaccine virus, particularly in ≥ 60 year olds receiving the vaccine for the first time [103,104]. Because of space limitations, for additional details on travel vaccines in the elderly the reader is referred to a recent review [102]. A summary of the vaccine trials that have been performed in elderly populations showing the paucity of data available, particularly regarding efficacy studies, is presented in Table 2.

Conclusions

The detrimental effects of aging on vaccination will increase in importance as a public health concern in the 21st century. Despite the relative paucity of vaccine studies in the elderly, general agreement exists that the immune response in the elderly is blunted and efficacy is lower compared to healthy young adults for most vaccines tested. In this chapter we have discussed some of the immune perturbations that can be attributed to immunosenescence. It is clear these immune defects need to be better characterized and then overcome with next generation vaccines.

Animal studies are informative and provide guidance for our understanding of the complexity of the human immune response during aging (see article by Maue et al. also in this issue). However, the unique nature of the human immune system and the many confounding variables that affect aged individuals call for caution in interpreting animal data

as a direct reflection of the mechanisms driving human immunosenescence. Indeed, we have repeatedly observed experimental vaccine constructs that worked well in animals, including non-human primates, but which have not performed well in human trials; importantly, these human trials were performed with healthy young adults and not in the elderly. One can predict that differences between animal and human responses to vaccination will only become more pronounced in the elderly. We fully concur with a recent article arguing that inbred mice can be used successfully as tools for elucidating basic immunology, but much less so as models of disease [105]. This notion is equally applicable to studies on immunosenescence, and in particular, on vaccine development in the elderly. Ultimately, proof of improved vaccines depends on clinical trials in elderly cohorts. We are hopeful that in the next few years geriatric vaccination will improve due to a better understanding of the mechanisms underlying human immunosenescence leading to clinical trials of novel vaccines, vaccine formulations, adjuvants, and vaccine delivery systems.

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Textbox 1

The opsonization and phagocytosis of pneumococci *in vitro* can be determined by a number of techniques [40]:

1. standard opsonophagocytosis (OPA) assay
2. killing-type OPA
3. phagocytosis of fluorescent bacteria by flow cytometry
4. uptake of radiolabeled bacteria

Textbox 2

"Seroprotection" in influenza is commonly defined as an HAI antibody titer of ≥1:40 while "seroconversion" is the achievement of a four-fold increase in HAI titer following immunization. However, laboratory-confirmed influenza infections may still occur in the elderly even in the presence of HAI titers ≥1:640[52]. Therefore, HAI titers are an imperfect correlate of immunity, especially for the elderly. Functional measures of antibody, such as virus neutralization, and qualitative measures, such as antibody subclasses and avidity, provide additional means to characterize the immune response to influenza vaccination.

Textbox 3

Factors other than age that might contribute to diminished immunity to hepatitis vaccination in the elderly:

- HLA haplotypes [87,88]
- Protein-calorie malnutrition [89]
- Vitamin B12 [90]
- Vitamin E [91]
- Zinc and selenium[92]
- Other trace elements[93]
- Thyroid disease[94]
- Injection into fat rather than muscle [95]
- Low dosage [96]

Table 1

SENIEUR Protocol: Inclusion and exclusion criteria for admission to immunogeriatic studies. (Adapted by Edelman from Ligthart [24])

INCLUSION CRITERIA	
1.	Men and women 65 years of age or older
2.	Community-dwelling
3.	Stable chronic non-immunologically mediated conditions (e.g., osteoarthritis, hypertension)
4.	Normal range of reference laboratory for: complete blood count and differential, thyroid stimulating hormone, serum vitamin $B_{12,}$ folate, vitamin E, AST/SGOT and ALT/SGPT, albumin, fasting blood glucose, blood urea nitrogen and serum creatinine
EXCLUSION CRITERIA	
1.	History or clinically apparent immunologically mediated chronic conditions (e.g., rheumatoid arthritis, lupus erythematosus)
2.	Immunodeficiency
3.	Severe respiratory disease requiring supplemental oxygen
4.	Psychiatric disorder, untreated or not in remission
5.	Infection within 2 weeks of immunization
6.	Inflammatory processes such as known chronic infections, inflammatory bowel disease or Westergren sedimentation rate (>50mm/hour for men, >60mm/hour for women)
7.	All malignancies (excluding non-melanotic skin cancer) and lymphoproliferative disorders diagnosed or treated actively during the past 5 years
8.	Arteriosclerotic event during the 2 weeks prior to enrollment (e.g., medically documented myocardial infarction, stroke, recanalization of the femoral arteries, claudication, or transient ischemic attack)
9.	Cardiac insufficiency, if heart failure present (New York Heart Association functional class III or IV)
10.	Poorly controlled hypertension (SBP ≥180mmHg, DPB ≥100mmHg)
11.	Renal Insufficiency (serum creatinine ≥2.0 or BUN ≥40)
12.	Elevated or low glucose (fasting ≥140 or <70; non-fasting >200)
13.	Cognitive impairment: score of <23 on the Folstein Mini-Mental State Examination.
14.	Depression or mood alteration: score of ≥6 on the Geriatric Depression Scale (ref)
15.	Malnutrition as defined by clinical judgment and by decreased serum albumin (<3.2g/L) or hypercholesterolemia (<160mg/dL), or low total lymphocyte count (<1500/ml^3).
16.	Anemia (Hct <30% or low serum vitamin $B_{12,}$ folate or vitamin E level)
17.	History of or current alcoholism or consuming >2oz of ETOH/day; current drug abuse; currently smoking ≥10 cigarettes per day.
18.	Medication exclusions include prednisone >5 mg/day (or equal), colchicines, imuran, methotrexate, azathioprine, cyclophosphamide, cyclosporine, or interferons.

Table 2

Current Recommendations for Vaccines in the Elderly (Age ≥ 65 years)

VACCINE	Recommended frequency	Studies in elderly	Evidence of efficacy in the elderly	Reference
Pneumococcal (PPV)	Once at age ≥ 65 yr	+	+/−	[35,38,37]
Influenza	1 dose annually	+	+/−	[46,45,1,47]
Tetanus, diphtheria	1 dose Td every 10 yr	+	+	[71,72,73,74,29]
Herpes Zoster	Once at age ≥ 60 yr	+	+	[106]
Hepatitis B	High-risk[1,2]	+	+	[107,82,108,81,80,78,79]
Measles, Mumps, Rubella	High-risk[1,2]	−	NA	
Hepatitis A	High-risk[1,2]	+	NA	[109,110]
Meningococcal	High-risk[1,2]	+	NA	[100]
Japanese Encephalitis	Travel[2]	+/−	NA	[111]
Typhoid (polysaccharide)	Travel[2]	−	NA	
Typhoid (oral, live)	Travel[2]	−	NA	
Polio	Travel[2]	−	NA	
Yellow Fever	Travel[2]	−	NA	
Rabies	Travel[2]	+/−	NA	[112]
Cholera	Travel[2,3]	−	NA	
Tick-borne Encephalitis	Travel[2,3]	+	+	[74]

Studies done in the elderly were: (+) done, (+/−) not specifically done in this age group, (−) not done.
The evidence of clinical efficacy in the elderly are: (+) clear, (+/−) not clear, (NA) information not available based on the lack of specific studies in the elderly.

[1] High-risk situations include certain medical, occupational, or lifestyle indications.

[2] Travel to areas with high endemic rates for the infection.

[3] Vaccine not available in the U.S.