Immunosenescence and Vaccination in Nursing Home Residents

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The elderly population continues to increase in most countries. Concomitantly, the number of individuals who are institutionalized is also increasing, unfortunately, with more and more individuals being institutionalized at greater ages. These elderly individuals are very different from healthy, community-dwelling elderly individuals, in that many are considered to be frail and have various chronic diseases. It is apparent that the immune response diminishes even in healthy elderly people and that the pathologies that occur in nursing home patients, together with malnutrition, further impair immunity required for an effective vaccine response. Therefore, it is important to take secondary age-related effects, attributable to factors such as chronic diseases, inflammation, frailty, nutrition, functional status, and stress, into account when assessing vaccination strategies. Despite these alterations that can affect immune function and their potential interaction with vaccination, vaccination is still worthwhile and is recommended for elderly nursing home residents. Research efforts should continue attempts to elucidate the immunological basis of impaired immunity in nursing home residents to design improved prevention strategies for this vulnerable group.

Older adults represent an increasing sector of the population, and institutionalization is becoming increasingly more common throughout the world [1]. The prevalence of infections (such as respiratory, skin and soft-tissue, and urinary tract infections) in nursing homes ranges from 1.6% to 32%, and overall incidence rates vary from 1.8 to 13.5 infections per 1000 resident-days [2]. In this population, age, as well as comorbidity and malnutrition, may reduce the immune response and thereby impair vaccine efficacy, which requires an adequate immune response [3]. In this article, we review the immunological changes commonly found in nursing home residents and summarize vaccine efficacy studies involving elderly nursing home residents.

IMMUNOSENESCENCE

The detrimental changes that occur in the function of the immune system with age are called immunosenescence. Each component of immunity is affected, although T cells appear to be most susceptible [4]. It is still controversial whether these changes occur as a pathological process or as a part of the normal physiological aging process. For example, in one study, diminished T cell proliferation, IL-2 production, antigen recognition, a shift in T cell subpopulation type, and cytokine production were found to be present in a healthy elderly population [5].

Although the exact causes of immunosenescence are not clear, it is becoming accepted that the multifactorial process of immunosenescence in the healthy elderly population correlates with certain universally observed processes, including thymic involution, chronic antigenic stimulation (predominantly attributable to persistent infections), signal transduction changes in immune cells, and protein-energy malnutrition.

Vaccine-Relevant Factors contributing to T Cell Immunosenescence

Thymic involution. In both experimental animals and humans, there is a decrease in thymus volume and cellularity,
thymocyte proliferation, and emigration of T cells to the periphery beginning at puberty [6]. These alterations result in decreased production of naive T cells awaiting priming by newly-encountered antigens.

**T cell subpopulation changes.** Aging is also associated with a shift from naive T cells to their memory counterparts, which have encountered antigen and undergone clonal expansion or contraction, becoming effector or effector-memory T cells. In addition to thymic involution, the observed increase in the numbers and proportion of such CD8+ T cells may be attributable to a repetitive infectious challenge, mainly by persistent viruses, notably cytomegalovirus [7, 8]. In fact, homeostasis of the immune system requires that, after stimulation, the clonally expanded population dies by apoptosis, which is a process that is decreased with aging. Reduced apoptosis could be the consequence of chronic antigenic stimulation or an adaptive phenomenon to avoid overactivation of these CD8+ memory cells. Together, these changes may lead to a shift of T cell subpopulations towards a dominant population of anergic memory CD8+CD28− T cells (effector and effector-memory phenotypes) in elderly individuals. These observed changes are also reflected in the patterns of proinflammatory cytokines produced by the T cells (so-called “inflammaging”) [8, 9].

**T cell signal transduction changes.** T cells sense external stimuli mostly via receptors on the T cell surface. The most important receptor is the highly polymorphic, antigen-specific T cell receptor/CD3 complex, which delivers the so-called “signal 1” for T cell activation [10]. With aging, there is an alteration of T cell signalling either in signal 1, signal 2 (costimulator activation), or both, as well as signal 3 (cytokines present), as described above. There are many age-related alterations in the signalling cascade of T cells, including calcium metabolism, tyrosine kinase phosphorylation, and protein kinase C translocation to the membrane. Moreover, it was recently demonstrated that there are alterations in the very earliest stages of the signalling cascade (i.e., in the composition and functions of the membrane rafts) [11]. These changes underline the functional changes observed in T cells with aging, in which various subpopulations of T cells are differentially affected. CD4+ cells are most affected, whereas CD8+ T cell reactivity is better maintained than that of CD4+ T cells [12].

**The Effects of Innate Immune Response, Nutrition, and Hormones on T Cells**

In addition to the intrinsic alterations in T cells, the homeostatic milieu of the aging organism also affects T cell functions and contributes to immunosenescence. However, the exact roles of each of these factors, as well as their interactions, are not fully elucidated.

**Innate immunity.** The innate immune system modulates adaptive immunity in several ways. The primary interaction occurs via antigen-presenting cells that are primarily dendritic cells, but that also include macrophages, B cells, activated T cells, and even neutrophils. The antigen-presenting capacity of the cells of the innate immune system per se does not seem to change markedly with age, but the capacity for immune synapse formation (interaction between antigen-presenting cells and T cells) is altered. This may be partly attributable to an alteration in the membrane properties and costimulatory molecules of the cells of the innate system with aging [13].

The innate immune system also influences the adaptive immune response by the timing, type, and amount of soluble mediators (cytokines) produced [14]. Toll-like receptors play a crucial role in innate modulation of adaptive immune responses. As discussed above, aging is associated with an increase in the production of proinflammatory cytokines [8], which is perhaps the price that must be paid to maintain essential immune surveillance against persistent pathogens [15]. However, there is no data to date that shows that changing this low-grade chronic inflammatory state would lead to a different biological or physiological outcomes in elderly subjects.

**Nutritional status.** In addition to pathogen load, nutritional status is a major factor influencing T cell responses [3, 16]. Even healthy elderly subjects who live at home often experience subclinical protein-energy malnutrition and/or micronutrient deficiency (mainly zinc deficiency), but protein-energy malnutrition is much more common among nursing home residents. The effects of protein-energy malnutrition on T cell function in younger people are almost identical to those observed in healthy elderly individuals: namely, a decrease in delayed-type hypersensitivity, IL-2 production, T cell proliferation, and antibody responses [17]. Micronutrient deficiencies may also play a role. A recent study involving nursing home residents found that subjects with low zinc concentrations had a lower incidence of pneumonia, a shorter duration of pneumonia, and fewer days of antibiotic use than did those with normal final serum zinc concentrations [18]. In one study [19], 200 IU of vitamin E supplementation administered to elderly nursing home residents significantly reduced the risk of acquiring upper respiratory tract infection. Another micronutrient receiving increased attention for its role in host defenses is vitamin D. Toll-like receptor–mediated mechanisms appear to be most vulnerable to subclinical vitamin D deficiency [20]. Therefore, vitamin D may have particular relevance to frail older adults with limited exposure to the sun who do not receive supplementation. Lipids may also have important immunomodulatory effects, especially polyunsaturated fatty acids, which regulate the inflammatory process and response [21].

**Hormones.** The immune system is part of the larger neuroimmune-endocrine system; most known hormones have immunomodulatory effects [22]. With aging, changes in endo-
crine system functions involving mainly dehydroepiandrosterone (adrenopause), growth hormone (somatopause), and sex hormones (menopause) occur and may impact immune function [22, 23]. Thus, this raises the question of whether hormone supplementation can improve immune function in the elderly. Some hormones, like dehydroepiandrosterone, oestrogen, melatonin, growth hormone, and insulin-like growth factor 1 have been shown to have varying effects on the aging immune system. Some others, like vitamin D and insulin, have not been investigated systematically.

**IMMUNE RISK PROFILE**

It is often difficult to separate the role of aging, per se, from that of chronic diseases in the immune dysfunction of older adults [2, 24]. A high burden of chronic disease may lead to impaired immunity, and impaired immunity may lead to a high burden of chronic disease. It is likely that interactions occur in both directions (figure 1). Recent studies [25] of the burden of chronic diseases have used the cumulative illness rating scale to address this issue [26]. The presence of 1 or 2 chronic illnesses, such as emphysema, diabetes, or chronic renal insufficiency, is associated with a 40-fold to 150-fold increase in the incidence rate for influenza or pneumonia [27]. On the other hand, although some studies have demonstrated a correlation between inadequate antibody response to influenza vaccination and chronic disease burden in elderly nursing home residents [27], many others have failed to demonstrate an association [28].

Longitudinal studies may help to elucidate some aspects of the complex interaction between aging and chronic diseases [29, 30]. These investigations, which grouped elderly individuals on the basis of whether they were in good health and or in poor health, were aimed at identifying factors predicting 2-year, 4-year, and 6-year mortality and resulted in the emerging concept of an “immune risk profile” (IRP). High CD8+ cell, low CD4+ cell, and poor T cell proliferative response were associated with the IRP that predicted higher mortality at follow-up. Most interestingly, cytomegalovirus seropositivity and large increases in the number of CD8+CD28+CD57+ T cells, which are known to be associated with cytomegalovirus carrier status, were significantly associated with the IRP [6], which was also independent of health status. Moreover, this increased number of CD8+CD28+ T cells, which is part of the IRP, predicted poor responses to influenza vaccination [31]. However, the IRP has not been studied in the nursing home setting.

**ADDITIONAL INFECTION RISK FACTORS FOR ELDERLY NURSING HOME RESIDENTS**

Nursing home residents are at additional risk merely by being in the nursing home environment. Outbreaks of several infectious diseases, including the common cold, norovirus, and *C. difficile* colitis, as well as the vaccine-modifiable illnesses of influenza, pneumonia, and even herpes zoster have been described [2, 26, 32–35]. Sharing sources of air, food, water, and medical care, as well as sharing caregivers, facilitates both the introduction and the subsequent transmission of certain infectious agents among the vulnerable residents, as has been elucidated by Strausbaugh and colleagues in a recent review [36], and influences immunization practices, as described below. The effect of individual factors on immune status and infection risk, particularly for vaccine-modifiable illness, requires further study. Risk models that account for these en-
vironmental factors, composite comorbidity measures [25, 26], and specific measures of immune function [29–31] may be of value.

**CLINICAL EFFICACY OF VACCINES FOR RESIDENTS OF LONG-TERM CARE FACILITIES**

Immunization against influenza is considered to be the cornerstone for prevention of respiratory infection in nursing homes. In a systematic review, influenza vaccine was found to be 23% effective in reducing influenza-like illness when vaccine matching was good, but it had no statistically significant effect when matching was poor or unknown [37]. The efficacy of the vaccines against laboratory-confirmed influenza was not statistically significant, but there was a large effect of well-matched vaccines in preventing pneumonia (vaccine efficacy, 46%; 95% CI, 30%–58%), preventing hospital admission for influenza and pneumonia (vaccine efficacy, 45%; 95% CI, 16%–64%), and preventing all-cause mortality (vaccine efficacy, 60%; 95% CI, 23%–79%). However, empirical evidence exists for the role of bias inflating the effectiveness of inactivated influenza vaccine in adults ≥70 years of age [38]. One study found that the relative risk of death or hospitalization among elderly individuals that was associated with influenza vaccination was lower before, during, and after the influenza season [39]. The same authors demonstrated that functional limitations appear to be important confounders. Another analysis found that mortality rates among older adults after the early 1980s remained virtually unchanged, despite increased vaccination coverage. The authors hypothesize that very ill elderly people, whose fragile health would make them highly likely to die over the winter months, are less likely to be vaccinated during the autumn vaccination period [40]. Frailty selection bias and use of nonspecific outcomes, such as all-cause death, have led to cohort studies that have exaggerated the effect of influenza vaccination [41]. Although the effect of such study bias is greatest in studies that involve elderly individuals who reside in the community, it is likely that the effectiveness vaccination has been distorted to some extent in studies involving nursing home residents, but specific data do not exist for this population.

Influenza vaccination of nursing home health care workers is also an important preventive health measure. Data from 2 cluster-randomized clinical trials have shown benefit [42, 43]. A systematic review concluded that staff vaccination had a significant effect on influenza-like illness (vaccine efficacy, 86%; 95% CI, 40%–97%), but protection was only found when residents were also vaccinated [44]. In a subsequent trial, nursing home staff members were offered vaccination in the intervention facilities or no vaccine in the control facilities [45]. Vaccine coverage of staff was 33–48% in intervention facilities and 4%–6% in control facilities over the study seasons. During a season of moderate influenza activity, the intervention was associated with a statistically significant reduction in mortality in the intervention facilities, compared with the control facilities (rate difference, −5.0 deaths per 100 residents; 95% CI, −7.0 to −2.0 deaths per 100 residents) and in influenza-like illness (P = .004).

Evidence for the direct benefit of pneumococcal vaccination in the elderly population has been controversial. Overall, randomized, controlled trials show that the risk of invasive pneumococcal disease is reduced, with a pooled estimated OR of 0.26 (95% CI, 0.15–0.46), which correlates to a protective vaccine efficacy of 74% (95% CI, 56%–85%) [45]. When data from adults with high-risk medical conditions were analyzed, there was no statistically significant protective efficacy against invasive pneumococcal disease. However, there was insufficient power to actually demonstrate an effect. The single randomized, controlled study that involved a long-term care facility excluded individuals who were considered to be at very high risk (those ≥85 years of age, those with comorbidities, and those who were bedridden) and, therefore, did not include those residents at highest risk (e.g., individuals with chronic obstructive pulmonary disease or bronchogenic cancer) [46]. Evidence of protective efficacy against invasive pneumococcal disease was shown in 4 studies involving community-dwelling elderly people (OR, 0.20; 95% CI, 0.10–0.41) [45]. For all-cause pneumonia and mortality, the pooled randomized trials failed to show an effect of the vaccine for these outcomes in either high-risk participants or healthy adults. However, the wide confidence intervals suggest insufficient power. Seven observational studies were assessed in this review. A subgroup analysis of only data from immunocompetent older adults included 5 studies showing that the polysaccharide pneumococcal vaccine reduced the risk of invasive pneumococcal disease, with a pooled estimated OR of 0.32 (95% CI, 0.22–0.47) [45].

**IMMUNOGENICITY STUDIES AND CORRELATES OF VACCINE PROTECTION IN THE NURSING HOME POPULATION**

Although an early decrease in protective antibody levels is frequently raised as a concern with respect to the timing of vaccination of elderly individuals with inactivated influenza vaccine, a recent review of the evidence suggests this may not be an issue [47]. The effect of primary antibody response appears to be a more important factor in this age group. The Committee for Propriety Medicinal Products, which is a committee that has responsibility for scientific opinion on human medicines for the European Medicines Agency, establishes threshold levels for seroprotection for the annual influenza vaccine used in the elderly population. The levels recommended by the Committee for Propriety Medicinal Products were maintained for ≥4 months by the elderly population in all 8 of the studies of influenza H3N2 and in 5 of the 7 studies of influenza H1N1
and influenza B. In all 8 of the studies of influenza H3N2, in 5 of the 7 studies of influenza H1N1, and in 3 of the 7 studies of influenza B, the higher seroprotection thresholds established for vaccine approval for young adults were also met by the elderly population for >4 months. If the goal established by the Committee for Propriety Medicinal Products was achieved initially after immunization, seroprotection rates of 70%–100% were maintained for at least 4 months (in 2 studies), 5 months (in 2 studies), and even >6 months (in 4 studies) for the influenza H3N2 and influenza H1N1 vaccine components [47].

There is some evidence that T cell responses may be better correlates of influenza vaccine protection in the elderly population than are antibodies. In a study that prospectively evaluated serum antibody titers, development of influenza infection, and cellular immune response in elderly participants, antibody titers obtained before and after vaccination with the trivalent influenza vaccine did not distinguish the 9 participants who developed influenza from those who did not [48]. In contrast, PBMCs restimulated ex vivo with live influenza virus preparations showed significant differences between infected and uninfected participants with respect to IFN-γ and ILN-10 ratios and granzyme B levels.

There have been several studies that, on the basis of antibody titers, have demonstrated poor immunogenicity to inactivated influenza vaccine in nursing home residents. In a recent study involving 120 nursing home residents, in which a 4-fold increase in HI titers was considered to be a positive outcome, a response was obtained in only 31% of the population [49]. Other antibody criteria for protection could not be assessed. The presence of dementia was the only variable associated with lack of response in multivariable analysis.

With respect to pneumococcal immunogenicity, in a recent study, 118 elderly nursing home residents received either the pneumococcal vaccine or a tetanus control vaccine [50]. Serum samples were obtained at study enrollment, at 2 months, and at 2 years after vaccination. Prevaccination antipneumococcal antibody geometric mean concentrations were similar in both study groups, with increased levels of antibody found only for serotype 14. The pneumococcal vaccine was highly immunogenic at 2 months, and titers remained high 2 years after the vaccination for the 10 serotypes studied in this elderly population.

**CONCLUSIONS AND PRIORITIES FOR RESEARCH**

Nursing home residents are at high risk of infection because of immunosenescence, multiple comorbidities, nutritional deficits, and environmental exposures. Vaccine-preventable infections are common, but vaccine efficacy is diminished in this population because of the factors listed above. Specific correlates of vaccine protection are not known, and identification of appropriate surrogate markers would greatly facilitate research [51].

Three vaccines—influenza vaccine, pneumococcal polysaccharide vaccine, and herpes zoster vaccine (plus diphtheria-tetanus boosters)—are specifically recommended by the Centers for Disease Control and Prevention for adults ≥65 years of age [52]. Given epidemiological evidence that vaccination involves some benefit, it seems prudent to recommend that both nursing home staff and residents receive annual influenza vaccination. However, because many elderly individuals respond suboptimally to vaccination, chemoprophylaxis should be used during outbreaks. New vaccine trials would be greatly facilitated by identification and validation of biomarkers and/or correlates of protection to determine who would most benefit from vaccination and who should receive alternate prevention measures. Sparse data exist on the efficacy of pneumococcal vaccination of nursing home residents, particularly those who are at highest risk for illness. Randomized trials are unlikely to be performed, given the huge number of subjects who would be required, but indirect cohort analyses may yield relevant data. Finally, there are no data on the efficacy of herpes zoster vaccination of nursing home residents, and there is scant published opinion [35]. However, the Centers for Disease Control and Prevention does not exclude nursing home residents from their broader recommendation [52], as long as no other contraindications exist.

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