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# Immunosenescence and vaccine failure in the elderly: Strategies for improving response

Diana Boraschi[a,*], Paola Italiani[b,1]

[a] Institute of Protein Biochemistry, National Research Council (CNR), 80131 Naples, Italy
[b] Institute of Biomedical Technologies, CNR, 20090 Segrate, Italy

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ABSTRACT

The immune system of the elderly is particularly susceptible to infectious diseases and displays reduced response to vaccination. The current vaccines, designed for young and adult individuals, proved less effective and less protective in old people. The world population is rapidly ageing, and consequently preventing infectious diseases in the elderly have become an important public health issue. To this end, it is necessary to develop novel vaccines especially suited to raising protective immunity in the ageing population. Approaches in this direction include high-dose vaccines, booster vaccinations, different immunisation routes, and use of new adjuvants. These approaches, still empirical, must be supported by intensive research to unravel the biological and molecular mechanisms underlying immunosenescence. Only this knowledge would allow us to design approaches to immune rejuvenation and more effective vaccines for protecting the elderly.



## 1. Introduction

Life expectancy has impressively increased during the last century worldwide, and is equally evident in developed and in developing countries. The United Nations expect that by 2050 about 25% of the world population will be >65 years of age, and that 75% of this elderly population will be living in developing countries [1].

One of the aspects that contributed to prolong life expectancy is the significant decrease in infectious diseases burden at young age, thanks to better nutrition, health care and effective preventive measures [2].

The elderly population is generally immunologically frail, and more susceptible to developing diseases. This becomes a major societal burden, as aged people may be in need of continuous assistance with great financial and psychological cost for the public health system and for the families. Ensuring healthy ageing ("adding life to years") is therefore a major public health issue. Increased susceptibility to diseases in the elderly is mainly due to immunosenescence, *i.e.*, the diminished effectiveness of the immune response. Thus, prevention of age-related immunological defects becomes a central issue for ensuring the individual well-being.

Among the consequences of immunosenescence, the increased susceptibility to infectious diseases is a major threat and cause of death also in developed countries. Vaccination has been the most successful preventive tool in preventing infections and infant death. However, the vaccination strategies that are currently and successfully used may not be suited for efficiently protecting the elderly population. The aged immune system does not react with the same rules as that of a child or a younger adult, thus current vaccines are in general less immunogenic and therefore less efficient in the elderly. Research on immunological ageing is addressing the fine mechanisms of age-related change in the immune regulation, aiming at providing the basis for designing efficient strategies for immune rejuvenation and for effective vaccines. However, it should be noted that most of these studies are performed in the mouse. The evolutionary distance between mice and men has introduced differences that do not always allow simple extrapolation of findings. This concept is particularly relevant if

*Abbreviations:* DC, dendritic cells; TLR, Toll-like receptors; TCR, T cell receptor; VZV, Varicella Zoster Virus; HIA, haemagglutination inhibition antibodies; HA, haemagglutinin; Tdap, tetanus/diphteria/acellular pertussis vaccine; TIV, trivalent inactivated influenza virus vaccine; APC, antigen-presenting cells; MVA, Modified Vaccinia Virus Ankara; NP, nucleoprotein; M1, matrix protein 1.

* Corresponding author at: Institute of Protein Biochemistry, CNR Area della Ricerca di Napoli 1, Via Pietro Castellino 111, 80131 Naples, Italy.
Tel.: +39 081 6132623; fax: +39 081 6132277.
*E-mail addresses:* d.boraschi@ibp.cnr.it, diana.boraschi@gmail.com, boraschi@altaweb.eu (D. Boraschi), p.italiani@ibp.cnr.it (P. Italiani).
[1] Present address: Institute of Protein Biochemistry, CNR Area della Ricerca di Napoli 1, Via Pietro Castellino 111, 80131 Naples, Italy.

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we consider the immunological differences between species [3,4], including their immunosenescence features [5]. Future studies should therefore focus more on investigating age-related immunological changes in humans, to generate hypotheses that could be tested further in animal models [6].

We are just starting to understanding how the immune system ages in humans and identifying molecular pathways that can be targeted to specifically improve the responses to vaccination in the elderly. In this perspective, this review will give a brief overview on novel vaccination strategies aiming at improving efficacy in the elderly.

## 2. Immunosenescence

Immunosenescence is not synonymous with immunodeficiency. Although a decline of immunological functions is evident, there are elements of the system that are preserved (*e.g.*, $CD8^+$ T cell poly-functionality, number of resident macrophages) [7], while others are even increased (*e.g.*, innate/inflammatory cytokine production by macrophages) [8]. Therefore, it has been suggested replacing the term immunosenescence with "senescent immune remodelling" [9], which better implies the plasticity of the ageing immune system.

In addition to age-related remodelling, the metabolic changes of the ageing body (*e.g.*, increased presence of apoptotic cells) induce the immune system to change its "quiescent" state to a different level of basal activation. Consequently, the immune reactivity of healthy elderly people is qualitatively and quantitatively different from that of healthy adults. Thus, different "normal" thresholds should be considered in the healthy ageing population [10].

The elderly population is more susceptible than young adults to cancer, chronic diseases and infectious diseases, with a slower and less efficient recovery [11,12]. The reduced responsiveness of the aged immune system is responsible of both the reduced response to infectious and pathological events, and the suboptimal response to vaccination.

Both innate and adaptive immunity are affected by age. The changes in the immune response of the elderly are due to intrinsic defects within immune cells (that show altered phenotype and function [13–15]), and possibly to defects in the bone marrow and thymic stroma microenvironment [16]. Other influencing factors encompass changes occurring in the ageing body, such as increased cellular death [17], increased oxidative stress events [18], nutritional status [19,20], hormonal dysregulation [21], comorbidities [22], and chronic diseases (*e.g.*, diabetes, cardiovascular diseases) [23]. All these factors contribute to generate a basal chronic low-grade inflammation, termed "inflamm-ageing" that maintains innate immune cells, such as macrophages, in a permanent low-grade activation state [24]. This may cause excessive inflammation and tissue damage upon infectious challenges. The functions of dendritic cells (DC) also appear to be constitutively activated in people >65 years of age, although these cells are less reactive to challenges that activate the innate Toll-like receptors (TLR) [25].

Cells of the adaptive immune system are also less functional [5]. Both naïve T and B cells are still able to undergo renewal, but a preponderance of memory T and B cells has been observed [26,27]. Memory B cells show a limited repertoire diversity [28], so that in elderly individuals the antibody response to new antigens is quantitatively decreased, less efficient and with lower avidity [29]. Table 1 summarises the main current knowledge on age-related immunological changes. The different processes involved in immunosenescence have been excellently reviewed recently [52,67–69].

## 3. Current immunisation approaches in the elderly

It is important to assess, in a vaccine for the elderly, not only the vaccine efficacy, *i.e.* the ability of a vaccine to confer protection against a specific infection, but also its effectiveness, *i.e.* the ability of avoiding other related diseases. For instance, the seasonal influenza vaccine, by avoiding infection with the influenza virus, also decreases the incidence of respiratory and cardiac diseases consequent to influenza. The value of vaccines for the elderly therefore relies not only on efficacy but also on effectiveness, *i.e.* in the capacity of generally improving the health status of the old individual.

In developed countries, four main vaccines are recommended for the elderly, in order to protect them from the most common infections: the seasonal influenza vaccine, the pneumococcal vaccine (against *Streptococcus pneumoniae*), the vaccine against tetanus, diphtheria and pertussis (booster every 10 years), and the vaccine to prevent reactivation of Varicella Zoster Virus (VZV).

These infections still represent a cause of significant morbidity and mortality in the elderly ($\geq$65 and $\geq$85 years), who are more susceptible to them compared to young adults [70–72]. Table 2 summarises the features of vaccines against these infections and their effects on the elderly immune system.

Of the four vaccines mentioned above, only the Tdap vaccine ('tetanus toxoid, reduced diphtheria toxoid and acellular pertussis') gives a satisfactory although diminished protective antibody response in the elderly compared to adults [73]. In contrast, vaccines against influenza or pneumococcal infections do not induce protective immunity in a large proportion of the elderly population, although they can mitigate the disease to some degree [74]. Similarly, vaccination with the live vaccine against VZV is only partially active in preventing reactivation of herpes zoster or attenuating the severity of post-herpetic neuralgia [75].

To understand why these vaccines are not fully effective in the elderly, one must take into account the following considerations:

1. these vaccines have been developed for preventing infections mainly in childhood and in immunologically competent individuals, and therefore they may not be optimally effective in the elderly that are immunologically different;
2. assessing vaccine efficiency in the elderly has been often difficult because of little consensus between studies (lack of study protocol standardisation), the use of outcome measures with low sensitivity (influenza-like illness rather than laboratory confirmed influenza), and insufficient consideration of frailty and study bias, varying cohorts and variable epidemiological factors (*e.g.*, in the case of influenza, prevalence of the virus, virulence of the circulating strain and matching of vaccine and circulating viral strain);
3. the extent of the immune response depends on intrinsic immunosenescent defects as well as on the history of natural exposure to pathogens or previous vaccines, both contributing to the baseline immune status of an older individual [76].

Optimising vaccination for the elderly is therefore a major task in immunological research [77]. The strategies to address the limitations of the current vaccines in protecting the elderly are illustrated in Table 3. We will briefly discuss them hereafter, taking the vaccine against seasonal influenza as an example, given the abundance of available data for this vaccine.

Since the understanding of the mechanistic basis of immune senescence is still partial, no current vaccination strategy is based on such knowledge and the approaches have been exclusively empirical. The most developed approaches include the use of higher