The global challenge and future strategies for keeping the world’s aging population healthy by vaccination

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The world’s aging population problem

The world’s population is aging in both economically advanced and developing countries, dramatic rises are predicted in the coming decades, and in some countries the number of elderly already outweigh the number of children. WHO has therefore defined the prevention of infectious diseases in the elderly as a global priority. Human evolution has not prepared mankind for aging beyond our reproductive years, and the ongoing immune response to antigenic stimulation with increasing age leads to a decline in immune function in a process called immunosenescence.

Infections are a major cause of morbidity and mortality in the elderly, and vaccination offers an ideal preventative tool. Only a handful of vaccines are currently recommended in vacci

Declining adaptive immunity in the elderly

Poorer vaccine responses and vaccine efficacy in the elderly

The elderly mount considerably poorer antibody and cell mediated immune (CMI) responses to vaccination, leading to irreversible cellular and molecular damage. Inflammaging is thought to be caused by the cumulative lifetime exposure to anti-

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poorer protective efficacy. For example, influenza vaccination is less effective in the elderly, reducing hospitalisation for influenza or pneumonia by 27% in a study spanning >700 000 person-seasons among community dwelling elderly in the US, and reducing death from all causes by 48%. This compares poorly with the 70–90% efficacy observed in young adults. Antibody responses to influenza vaccination are impaired, and repeated vaccination fails to increase antibody avidity. Primary T cell responses to vaccination are particularly affected, whereas memory CD4+ and CD8+ T cell responses induced earlier in life remain relatively intact.

The efficacy of the 23-valent pneumococcal polysaccharide vaccine (PPV) wanes with increasing age, and seems to provide little protection against non-bacteraemic pneumococcal pneumonia in the elderly. PPV is a T cell independent vaccine and several studies show that pneumococcal antibody responses decline with age, while avidity remains comparable to younger adults. Thus the lack of protection is likely due to declining humoral immunity with age. The T cell dependent pneumococcal conjugate vaccine (PCV) was more immunogenic than PPV in the elderly. It is therefore widely recommended that a dose of PCV-13 be given in those >65 years of age, followed by PPV-23 6–12 months later.

Pertussis is a common infection among adults in wealthy countries, accounting for a high percentage with chronic cough, and high complication rates in the elderly. Vaccine-induced immunity lasts 5–10 years and many elderly are non-immune. Failure to mount protective antibody levels to tetanus and diphtheria are frequent in the elderly, but is better among those with higher pre-existing antibody levels. Antibody responses and seroconversion rates to hepatitis B vaccine also decline with age, thought to be due to the combination of B and T cell immune dysfunction.

Healthy humans can be infected with as many as 12 latent viruses including cytomegalovirus, which is associated with high levels of CD8+ T cells that lack expression of CD28 implicated in causing poor antibody responses to influenza vaccine in the elderly. The cost of maintaining reactivity to chronic viruses may be reduced reactivity to new antigens including those in vaccines.

Declining innate immunity with age is also likely to have a significant impact of efficacy of live vaccines. Many live vaccines, such as bacillus Calmette Guérin (BCG), measles and yellow fever vaccines, contain intrinsic innate ligands or pattern associated molecular patterns (PAMPs) which trigger an early innate inflammatory response via pattern recognition receptors expressed by immune cells, such as the toll-like receptors (TLRs). Innate and adaptive immunity are tightly linked, indeed, early innate signatures to yellow fever vaccine predict later protective CD8 responses to vaccination.

**Heterologous non-specific effects of vaccines in the elderly**

Vaccines can have effects on the immune system beyond the induction of vaccine specific immunity. These have been called ‘heterologous’ or ‘non-specific effects’ of vaccines, and lead to altered susceptibility to other infections. Broadly, live vaccines such as BCG or measles vaccine can enhance immunity and increase protection against other infections, whereas inactivated vaccines such as diphtheria-tetanus-pertussis or hepatitis B vaccine increase risk of infection from non-targeted pathogens. The data regarding non-specific effects have been mainly limited to studies in children and there are no studies to date investigating their impact in an elderly population. This is an area of ongoing research by our group, and could play an important role in the poorer immunogenicity of vaccines with aging, and the increased susceptibility of the elderly to infections. Vaccine non-specific effects could also potentially be exploited to improve vaccine response; for example, using a live vaccine instead of an inactivated one to provide immune benefits beyond the induction of vaccine specific immunity, or combining live and inactivated vaccines. Indeed, a recent study showed that prior administration of BCG enhanced influenza vaccine antibody responses in healthy adults. Furthermore, we have recently shown that when live and inactivated vaccines are administered simultaneously to infants, the non-specific immunological profile is different compared to when the vaccines are given alone.

**Sex differences in immunity and vaccine responses in the elderly**

Women have a greater life expectancy than men, in part due to gender-specific effects such as lifestyle and risk-taking; with sex-specific effects such as X chromosome diploidy and sex hormones playing a major contributory role. The X chromosome encodes for multiple immune response genes and microRNAs that regulate gene expression, and sex hormones have multiple immunological effects with oestrogens generally promoting and androgens suppressing immune responses. In adulthood, females are thought to be immune-privileged compared to males, as exemplified by superior immunity and survival from multiple infections, and better responses to many vaccines compared to males. The menopause has distinct effects on the female immune system, and while women remain immune-privileged, they experience immunosenescence and a decline in their vaccine responses. Hormone replacement therapy (HRT) based on oestrogens may improve vaccine responses in elderly females, as has been demonstrated in several murine studies. Therefore HRT based approaches might be used to benefit vaccine immunogenicity in aging females. Vaccine non-specific effects have consistently been shown to be sex-differential in children, and it will be interesting to see if this is also the case in post-pubertal aging adults.

**Strategies for improved vaccines for the elderly**

We are only just beginning to understand how the human immune system ages, and to identify molecular pathways that might be targeted by vaccination. Strategies to improve vaccine efficacy have included the use of new adjuvants, different routes of immunization (e.g., intradermal), higher vaccine doses and boosters with limited benefits.
Due to the relatively poor immunogenicity of standard trivalent influenza vaccination (TIV) in the elderly, two new influenza vaccines were developed: an MF59-adjuvanted intramuscular vaccine called Fluarix (adjuvanted TIV or ATIV) and a non-adjuvanted intradermal vaccine called Intanza 15 mcg. Both elicit comparable antibody levels, which are higher than standard seasonal influenza vaccine, but effects on CMI are not known. ATIV was less effective than standard TIV in preventing hospitalisation for influenza or pneumonia in 65–74 year olds, but more effective in >75 year olds, but in another study TIV was ineffective in preventing influenza while ATIV was 60% effective. The development of a high dose inactivated trivalent influenza vaccine (IIV3-HD) has been another approach to improve immunogenicity in the elderly, with studies indicating superior immunogenicity and an approximate 24% relative efficacy compared to TIV in >65 year olds.

The live attenuated influenza vaccine (LAIV) is an intranasally administered live vaccine licensed for use in children and adults, which mimics natural infection more closely, eliciting a broader immune response including antibodies and cell-mediated immunity. It is not currently recommended for use in the elderly. A double-blind study comparing TIV+LAIV to TIV+placebo in elderly nursing home residents showed a 60% decrease (95% CI, 18–82%) in laboratory confirmed influenza A in the group receiving both vaccines. A study comparing LAIV, TIV, both vaccines together or placebo in elderly subjects suggested that the LAIV +TIV combination elicited comparable antibody levels to younger adults. A South African study compared safety and efficacy of LAIV and TIV in adults 60–95 years of age. Greater antibody responses were seen with TIV and better CMI with LAIV, but there were too few influenza cases to determine efficacy. It has been suggested that CMI is a better correlate of protection against influenza than antibodies in the elderly. Taken together these studies suggest that using a live vaccine may be another strategy for improved influenza vaccine efficacy in elderly people. However, other randomised trials suggest no advantage of LAIV over TIV in the elderly, thus further large randomised trials are needed.

Harnessing innate stimuli such as the TLR agonists have shown promise as vaccine adjuvants, and can overcome certain T cell defects. For example the TLR4 agonist glucopyranosyl A (GLA) has been shown to have effective and comparable adjuvant properties in elderly compared to younger humans. An influenza vaccine adjuvanted with the TLR5 ligand flagellin induced 75% seroconversion and 98% protection against influenza in 120 elderly subjects ≥65 years.

Evidence suggests that prebiotics and probiotics have immunomodulatory effects and may provide an inexpensive and readily accessible solution to enhancing vaccine efficacy in aging populations. When combining a short-term treatment with probiotics prior to influenza vaccination, post-vaccination levels of IgM, T helper cell and cytotoxic responses were higher in both adults and the elderly.

Conclusions
A better understanding of the mechanisms behind poor vaccine efficacy in the elderly is critical to finding strategies to improve vaccine efficacy and protect this vulnerable age group. Solutions are urgently needed since the current vaccines available are not adequate, and the worldwide population >60 years old is predicted to reach 2 billion by 2050. Improved uptake of vaccination in the elderly will also be required, and less developed countries may also wish to focus on this population in order to reduce the significant health burden the elderly age group presents. Clearly, inexpensive and practical solutions are needed for settings where resources are limited and the focus is on improving health and survival in children.

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