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Reference

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Review

Vaccine effectiveness in older individuals: What has been learned from the influenza-vaccine experience

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Abstract

Vaccination policies in most high-income countries attempt to reduce the adverse impact of influenza targeting people aged at least 60 years. However, while it is widely believed that the current immunization strategy saves many lives, influenza infection still remains a severe burden in aged individuals leading to a wide debate on the exact magnitude of the benefit of vaccination in this population. The first aim of the present review is to examine how effective current influenza-vaccine strategies are in aged adults, by analysing which are the most important factors modulating the interpretation of study results in this population. Furthermore, consideration will be given to how immune factors influence the measurement of vaccine efficacy/effectiveness, where advancing age leads to deleterious changes in the adaptive immune system, resulting in less than optimal responses to infectious agents and vaccination. Finally this review concludes with possible strategies to improve the ability of the senescent immune system to respond to vaccination.

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1. Introduction

Vaccine preventable diseases (VPDs) remain a severe burden in adult populations of developed countries (Michel and Lang, 2011). In the United States, they account for more than 70,000 deaths per year in these populations compared with 200 deaths in children (Poland et al., 2009). Aside from a 350-fold increased likelihood of death, VPDs are also associated with an age-related increase in serious adverse health events leading to hospitalization, debilitating complications and/or death (Michel and Lang, 2011). Deleterious changes in the adaptive immune system mainly associated with advancing age are major contributors to a less than optimal response either to the vaccination or to infectious agents (Aspinall and Goronzy, 2010).

Foremost amongst VPDs is influenza. Worldwide estimates indicate that influenza infections cause 3–5 million of severe cases per year resulting in 250,000–350,000 deaths (Influenza, 2008). In the European Union, between 40,000 and 220,000 deaths per year have been attributed to infection by influenza (Seasonal Human Influenza and Vaccination, 2010). The highest prevalence mainly occurs amongst older adults especially those with chronic medical conditions or immunological disorders, resulting in increased mortality in these high risk groups (World Health Organization, 2005). However, mortality is just the tip of the iceberg in terms of disease burden, as it can also act as a trigger for functional decline leading to disability in some aged individuals (Monte et al., 2009; McElhaney, 2005; Greenberg and Piedra, 2004; Gavazzi and Krause, 2002). Such outcomes represent a considerable economic burden amounting to $87 billion each year in the United States (Molinari et al., 2007). While it is widely believed that influenza vaccination saves many lives, prompting the widespread use of trivalent inactivated influenza vaccine (TIVs – 300 million doses produced each year) the exact magnitude of the benefit of the current immunization strategy in the aged population is still controversial (Jefferson, 2006; Fireman et al., 2009; Jackson et al., 2006a,b, 2008; Simonsen et al., 2007, 2009). This review will aim to examine how effective current influenza-vaccine strategies are in aged adults and analyse which are the most important factors modulating the interpretation of study results in this population. Furthermore, consideration will be given to how immune factors influence the measurement of vaccine efficacy/effectiveness. This review will conclude with possible strategies to improve the ability of the senescent immune system to respond to vaccination.
2. Is current influenza vaccine actually effective in aged individuals?

The current TIVs contain 15 μg of hemagglutinin (HA) of each of the three influenza strains (A/H1N1, A/H3N2 and influenza B). Humoral anti-HA antibody response is used as a surrogate marker for vaccine efficacy (Fiore et al., 2008). To assist in the interpretation of influenza vaccine immunogenicity, the Committee for Proprietary Medicinal Products (CPMP) describes a satisfactory HA inhibition (HAI) by serum anti-HA antibody response in the aged population (Note for Guidance on Harmonization of Requirements for Influenza Vaccines, 1997), as shown in Table 1, by one of the following criteria: (i) >60% achieving a reciprocal HAI titre of ≥40 (considered as seroprotection rate); or (ii) a mean geometric – GMT of HAI antibody increase in titres of ≥2.0-fold (the seroprotection rate); or (iii) >30% achieving a 4-fold rise in HAI antibody titre (the seroconversion rate). TIV prevents laboratory-confirmed influenza illness in approximately 70–90% of healthy adults below the age of 60 years in randomized controlled trials when the vaccine and circulating viruses are antigenically similar (Centers for Disease Control and Prevention, 2004; Jeffery et al., 2007). Whilst such protection occurs in young adults, the picture for the aged individuals is not clear and for obvious ethical reasons, it is not currently possible to resolve this issue by randomized placebo controlled trials, although this has been done in the past (Goveart et al., 1994). So the efficacy of the vaccine, especially in the elderly, has mainly been derived from observational studies typically using data from research databases or health care utilization data system (Nelson et al., 2009).

2.1. What are the estimates given from observational clinical and immunogenicity studies?

Observational studies have consistently reported reductions in all-cause mortality for vaccinated seniors during the influenza season (Nelson et al., 2009). These results have been interpreted by some as evidence that vaccination reduces the risk of death and influenza-related hospital admission in the elderly (Fiore et al., 2008) and have led to support of senior vaccination programs as both cost-saving (Deans et al., 2010; Macciose et al., 2006) and cost-effective (Nichol et al., 2007). Indeed, some studies have indicated that vaccination can be up to 80% effective in preventing influenza-related death (Monto et al., 2001; Jefferson et al., 2005; Patriarca et al., 1985), and up to 70% effective in preventing hospitalization for pneumonia and influenza for older persons living in an institutional setting (Nichol et al., 1998, 2007; Mullooly et al., 1994). However, questions have arisen about whether these benefits have been overestimated (Jefferson, 2006; Fireman et al., 2009; Jackson et al., 2006a,b, 2008; Simonsen et al., 2007, 2009). In a recent Cochrane systematic review, authors were unable to reach clear conclusions about the exact benefit of the vaccine strategy against laboratory-confirmed influenza cases or effectiveness against influenza-like illness (ILI) in aged individuals, due to the likely presence of bias in non-randomized controlled trials (Jefferson et al., 2010). Similarly, immunogenicity studies do not seem to provide clearer outcomes. The early decrease in primary antibody responses (i.e. anti-HA antibody responses induced in previously unvaccinated persons) had been noted in older adult populations compared to younger adults in two reviews (Goodwin et al., 2006; Beyer et al., 1989). However, both approaches highlight serious methodological flaws which include a failure to exclude participants with (i) conditions that have influence on the immune system; (ii) those previously vaccinated and (iii) those with high pre-vaccination titers (Skowronski et al., 2008) (see below).

2.2. Evidence of bias in estimates of influenza vaccine effectiveness

Some reports (Jefferson, 2006; Fireman et al., 2009; Jackson et al., 2006a,b, 2008; Simonsen et al., 2007; Nelson et al., 2009) suggest that selection bias may be responsible for the vaccine effectiveness (VE) estimates. It was reported that individuals selected for vaccination generally appeared “sicker” than unvaccinated individuals (Iezzoni et al., 2000; Chan et al., 1999; Xakellis, 2005; McGuire et al., 2007; Hak et al., 2002). However, recently from a cohort of 72,527 persons over 65 years of age followed over 8 years and incorporating a pre-influenza season analysis, Jackson et al. (2006a) demonstrated a preferential receipt of vaccine by relatively healthy seniors. This finding has also been noted by others (Jackson et al., 2006a,b, 2008; Simonsen et al., 2007; Nelson et al., 2009; Jackson, 2008) and a curvilinear relation between predictors of mortality and vaccination depicted (Fireman et al., 2009). Furthermore, functional limitations, such as requiring assistance for bathing, have been demonstrated to be associated with a decreased likelihood of vaccination even in aged persons free of comorbid conditions (Jackson et al., 2006b). All together, these recent findings suggest that near the end of life, disability appears as a contributing factor in the decision to receive or resist vaccination. Thus, pre-influenza season analyses seem to introduce biases that may not present in the influenza season analyses (Hak et al., 2006). Indeed, observational studies generally select subjects who are appropriate candidates for the intervention, who all have similar access to the intervention. Thus, persons known to have a short life expectancy may not be offered vaccine, and a person dying before the end of the vaccination period may have had fewer opportunities to get vaccinated compared to individuals who are relatively healthy throughout the vaccination season (Nichol et al., 2007). In addition, the retrospective assessment of functional status is also a finding leading to a healthy vaccine bias in observational studies (Jackson et al., 2006b). Moreover, additional findings from Fireman et al. (2009) showed that after having adjusted for risk factors, (i.e. older age, chronic conditions, and self-reported health status) mortality

<table>
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<th>Table 1</th>
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<td>Age-specific immunogenicity criteria established by the Committee for Proprietary Medicinal Products of the European Medicines Evaluation Agency, based on sera collected at baseline and 3 weeks after immunization.</td>
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<td>Immunogenicity criterion</td>
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<td>Mean geometric increase</td>
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HAI = hemagglutination inhibition.
before, during and after 9 influenza seasons increased by similar trajectory over time in both healthier and high-risk of death subgroups. This provides strong evidence that selection bias is a fatal flaw of many observational estimates in aged individuals and these results do not provide valid evidence on which to estimate the true benefit that may be derived from influenza vaccination.

2.3. How to differentiate vaccine effect from bias

To differentiate vaccine effects from bias, Fireman et al. (2009) has proposed a “difference in differences” approach. In other words, if the flu vaccine really does prevent deaths, then in a large population there should be a detectable difference between: (i) the difference in the odds of prior vaccination between decedents and survivors that is observed on days when influenza is circulating and (ii) the difference in the odds of prior vaccination between decedents and survivors that would be expected on the same calendar dates if influenza were not circulating. Hence, influenza vaccine effectiveness reduced all-cause mortality among aged adults by 4.6% (95% CI: 0.7–8.3) during 1996–2005 laboratory-defined flu seasons (Fireman et al., 2009). Whereas it has been found by Simonsen et al. that influenza infection accounted at most for 10% of all deaths during the influenza season (Simonsen et al., 2007), many cohort studies reported a 50% reduction in the total risk of death in winter (Nichol et al., 2007; Vooroud et al., 2003).

However, as recently discussed by Nichol, the accurate excess deaths/winter-time deaths ratio attributable to influenza is challenging to estimate, due to the lack of available individual-level measures (Nichol, 2009). This ratio uses a numerator that underestimates influenza-associated deaths due to the difficulty to understand the true disease burden caused by influenza and a denominator that over-estimates deaths during the influenza season (Nichol, 2009; Thompson et al., 2009). As a result, this ratio does not accurately reflect the absolute mortality burden attributable to influenza and is therefore a misleading number for judging the plausibility of influenza vaccine mortality benefit.

Similarly, in a recent large population-based nested case-control study, which incorporated a seasonally analysis, influenza vaccination was not significantly associated with a reduction in the risk of community-acquired pneumonia in the aged population (Jackson et al., 2008). While the VE estimate is consistent with approaches from two recent meta-analyses demonstrating the VE against pneumonia hospitalization (Rivetti et al., 2006; Vu et al., 2002), the width of its confidential interval demonstrates an imprecision and a lack of statistical power (Nichol, 2009).

Thus, the influenza vaccine benefits “controversy” arises from questions about whether residual confounding and bias in observational studies have resulted in VE estimates that misjudge the true benefit. Without dramatic modification the current adjustment methods will not adequately control for bias and the controversy will undoubtedly continue. New strategies are needed to improve the accuracy of influenza VE estimates. Future studies should include exploring the strengths and limitations of various comparison periods for model validation, the influence of important potential confounders, and other methods to quantify the impact of potential residual confounding such as sensitivity analyses (Nichol, 2009). Complementarily, approaches for reducing bias should include obtaining more accurate information on confounders, such as functional status and life expectancy, avoiding all-cause death in favour of outcomes such as pneumonia or influenza-related pneumonia, and include prospective ascertainment of influenza-specific outcomes to improve study sensitivity to detect a true vaccine effect (Nichol et al., 2009). Age-related changes in the immune system should be also considered. However, while immunosenescence is undoubtedly a very real and important phenomenon adversely influencing vaccine response (Grubek-Loebenstein et al., 2009; Fulop et al., 2009; Sambhar and McElhaney, 2009; Siegrist and Aspinall, 2009), how it should be measured and how it exactly influences changes in clinical protection is still unclear.

3. How immune factors may influence influenza vaccine efficacy/effectiveness estimates

3.1. Do pre-vaccination HA-antibody titres influence the vaccine response?

Most adults have pre-existing levels of antibody because of prior influenza infection and/or flu vaccination but this will vary in specificity depending on the age of the individual (Sasaki et al., 2008). Thus, young adults and elderly differ markedly for A/H1N1 strains (circulating between 1918 and 1957 and reintroduced in 1976), but are more similar for A/H3N2 strains (circulating since 1968). Older individuals with siblings infected during the influenza outbreak of 1918 possess highly functional, virus-neutralizing antibodies to the 1918 H1N1 virus, nearly 90 years after the pandemic (Yu et al., 2008). Complementarily, a cross-sectional serological survey conducted in 2008, before the first wave of A/H1N1 infection, showed a positive correlation between age and HAI and microneutralisation antibody titres to pandemic A/H1N1 (Miller et al., 2010). Similarly, prior year vaccination can also influence the HA-antibody and B-cell responses to re-vaccination. This has been demonstrated by Sasaki et al. (2008) in young healthy adults (age range 22–49 years) where differing influenza vaccination histories in the prior year and in which the serum antibody and B-cells to TIVs or life attenuated influenza vaccine (LAIV) were quantified during the 2005–2006 influenza season. Lower levels of baseline anti-HA titers were associated with a greater fold-increase of HAI titre and number of antibody secreting cells number after vaccination. This suggests that prior history of influenza infection and/or vaccination affects the serum HA-antibody and the B-cell responses to subsequent vaccination. As demonstrated by Feng et al. (2009), a similar picture is observed in the aged population regarding the proportional fold decrease in antibodies after vaccination to the pre-existing levels of HA-antibody. Thus, higher pre-immunization titres are associated with lower likelihood of demonstrating fold rises or seroconversion leading to the underestimation of vaccine efficacy whether the HAI titre is used as a surrogate marker of protection and the increase in HAI titre considered as a measure for predicting vaccine efficacy. These findings suggest that a clear inverse relationship exists between pre-immunization antibody levels and antibody increase after vaccination in elderly individuals and, that prior contact with either influenza virus or vaccine may severely influence the interpretation of HAI titer following vaccination in this population.

3.2. Is the protective HAI titre decline throughout the influenza season?

Although the early decrease in protective anti-HA antibody levels (within 4 months following vaccination) is frequently raised as a concern with respect to the timing of vaccination of elderly individuals (Smith et al., 2006), a recent review conducted by Skowronski et al. (2008) suggests this may not be an issue. Amongst the 14 studies included in this review, 8 reported seroprotection rates (Ruf et al., 2004; MacKenzie, 1977; Peters et al., 1988; Delafuente et al., 1998; Buxton et al., 2001; Brydak et al., 2003; Praditsuwan et al., 2005; Hui et al., 2006) and 6 seroconversion rates alone (McElhaney et al., 1993; Powers et al., 1995; Van Hoecke et al., 1996; Minutello et al., 1999; Myśliwska et al., 2004; Keylock et al., 2007). Seroprotection rates according to CPMP criteria (Table 1) were maintained ≥4 months after influenza immunization in all 8 for A/H3N2 com-
ponent and in 5 of 7 studies for the A/H1N1 and B components. In determining whether serological CPMP criteria were met at season’s end, seroprotection rates of 70–100% were maintained not just at 4 months (Delafluente et al., 1998; Buxton et al., 2001) but also at 5 months (Peters et al., 1988; Brydak et al., 2003) and, even at >6 months (Ruf et al., 2004; Mackenzie, 1977; Praditsuwan et al., 2005; Hui et al., 2006) for the A/H3N2 and A/H1N1 vaccine components. In 2 of 6 studies reporting seroconversion alone, criteria were still met at 4 months (Van Hoecke et al., 1996; Mysliwsk et al., 2004). Six studies had compared antibody persistence regarding the age with no significant difference between groups (3 compared elderly with young adults (Mackenzie, 1977; Brydak et al., 2003; McElhaney et al., 1993) and 3 compared aged individuals by advancing age (Peters et al., 1988; Praditsuwan et al., 2005; Van Hoecke et al., 1996)).

3.3. Does innate immunity play a role in the response to vaccination?

The primary interaction with the adaptive immune system is via the antigen presenting cells (APCs) and the decline in the numbers of these cells with age may impact severely on the strategies for coping with influenza. Further impact may follow because of the response to toll-like receptor (TLR) ligands. In a recent study, Panda et al. (2010) found substantial decreases in older compared with young individuals in TNF-α, IL-6, and/or IL-12 (p40) production in myeloid dendritic cells in response to TLR1/2, TLR2/6, TLR3, TLR5, and TLR8 engagement and TNF-α and IFN-α production in plasmacytoid dendritic cells in response to TLR7 and TLR9 engagement. Authors also found higher intracellular cytokine production in the absence of TLR ligand stimulation with APC from older compared with young individuals, suggesting some dysfunction in the regulation of cytokine production. Moreover they showed a strong association between poor antibody responses to influenza immunization and impaired TLR function in the older individuals.

3.4. What is the effect of the age-related expansion of dysfunctional terminally differentiated T-cells?

Quantification of T-cell numbers throughout the lifespan shows that they are maintained in old mice (Aspinall et al., 2010) and in humans even in their tenth decade (Mitchell et al., 2010) at levels which are comparable to those found in younger individuals. This would imply that there is no decline in the homeostatic mechanisms which preserves the size of the peripheral T-cell pool within defined boundaries. But such conservation may be achieved at the expense of the content. With the age associated reduction in thymic output and the proliferation of T cells driven either by antigen or cytokines, the constituent T-cells of the pool must be progressing towards their replicative limit with age. Evidence of this comes with CD28 expression. The CD28 marker is expressed on >95% of human T-cells at birth, but with age there is a progressive increase in the proportion of CD28– T-cells, particularly within CD8+ T-cell subset which is the major immune mediator of viral clearance (Effros, 2007a; Hünig et al., 2010). The proliferative capacity of CD28– T-cells is also limited, these cells have shortened telomeres, and show increased resistance to apoptosis and restricted T-cell diversity (Vallejo, 2005). Proliferation within the peripheral T-cell pool as we age may be unbalanced and this is particularly when persistent viral infection is involved. Infection with the Herpesviridae family including human β-herpes viruses and with poliomaviruses, may shape of the repertoire of the immune system with age (Weiskopf et al., 2009; Lang et al., 2009; Virgin et al., 2009). Whilst some reports suggest that localized, niche limited, latent herpes virus (HHV1) may not have any impact on immunosenescence (Lang et al., 2008), evidence implicates chronic cytomegalovirus (CMV or HHV5) infection in the age-dependent expansion of dysfunctional terminally differentiated T-cells (CD8+ CD28–). In CMV seropositive older adults, up to 25% of the total CD8+ T-cells pool can be specific for CMV immunodominant epitopes (Pawelec et al., 2009) and this expansion of CMV-specific CD8+ T-cells alters the capacity of the immune system to respond to other pathogens. These cells are able to secrete pro-inflammatory cytokines and contribute to an ongoing inflammatory process (Pawelec et al., 2009). The reasons for the putatively unique effects of CMV compared with other Herpesviridae and other pathogens are unclear at present. One possibility may reside in the cell types acting as CMV reservoirs and their intimate interactions with immune cells (i.e. antigen presenting cells such as DCs, as well as endothelial cells) (Pawelec et al., 2009).

4. How to improve the ability of the senescent immune system to respond to vaccination?

4.1. Is immunosenescence a quantifiable disorder?

Since the single preceding event in all cases of immunosenescence is thymic involution, can we identify a specific thymic rate of output which is linked to a state of immunosenescence? Studies to identify recent thymic emigrants (RTEs) have shown that the optimal means possibly uses a mixture of molecular and phenotypic techniques. Molecular techniques include PCR based assays of populations of cells for their content of signal joint T-cell receptor gene excision circles (sj-TREC) which are circular DNA products of T-cell receptor α chain rearrangement (Aspinall et al., 2000). Recent phenotypic moieties include protein tyrosine kinase 7 (PTK7) expression (Haines et al., 2009). PTK7 mainly identifies RTEs that are more recently produced by the thymus, PTK7+ naive CD4+ T-cells are uniformly CD31+ and a more pronounced and persistent loss of PTK7+ CD4+ than PTK7-CD31+ naive CD4+ T-cells is observed after complete thymectomy. Indeed, most adult circulating naive CD4+ T-cells are CD31+ and a CD31- subset describes lower sj-TREC content and less αβ-TCR diversity than CD31+ fraction and may be generated by foreign antigen-dependent homeostatic proliferation (Kohler et al., 2005). The use of a combination of markers to assess thymic output in older individuals has not been completed yet. However, recently, Mitchell et al. (2010) analysing peripheral blood mononuclear cells (PBMCs) from healthy individuals aged 60–104 years have shown an age-associated decline in sj-TRECs per 10^5 T-cells becoming significant during the 9th decade.

4.2. How to identify individuals who are poor responders

Predicting individual responsiveness to vaccination using biological markers that distinguish between healthy and immunosenescent states is desirable. However achieving this goal with a simple and robust method is very challenging. Trzontkowski et al. (2003) suggest that a single marker which could identify the functioning of one compartment of the immune system, without taking interaction with other components into account, might prove to be insufficient. Indeed they are often affected by a wide range of co-morbid conditions that influence the final outcome of the vaccination. Hirokawa et al. (2009) have proposed a T-cell immune score expressing the immune status of individuals as a simple numeral. This score combines five T-cell related parameters: number of T-cells, ratio CD4+ to CD8+ T-cells, number of naïve T-cells (CD4+ CD45RA+), ratio of naive to memory (CD4+ CDRO+) T-cells, and T-cell proliferative index (TCPI).

An alternative method has been to identify the immune risk profile (IRP), a condition consisting of high CD8+, low CD4+ numbers,
characterized by an inverted CD4+/CD8+ ratio and a poor mitogen response to concanavalin A (ConA) stimulation and, associated with persistent CMV infection leading to the expansion of dysfunctional terminally differentiated CD8+ CD28− T-cells (Pawelec et al., 2009; Strindhall et al., 2007). Interestingly, in an examination of immune parameters over the adult lifespan as a whole, Wilby et al. (2008) have observed (i) an increase in the prevalence of individuals having an IRP from about 8% in the age range of 20–59 years to about 16% in the age range of 60–94 years of age, (ii) a higher mortality rate in individuals above 60 years of age who have an CD4+/CD8+ inverted ratio, and (iii) a significant lowering of the numbers of CD3+, CD3+ CD4+ and CD3+ CD8+, and of CD8+ CD45RA+ CCR7+ cells across the adult lifespan. Complementarily, findings from the NONA immune longitudinal study confirmed the importance of the IRP as a major predictor of mortality and suggested that survival to the age of 100 years was associated with the selection of individuals with “inverted” IRP that was stable across the time (i.e. avoidance of inverted CD4+/CD8+ ratio and low numbers of CD8+ CD28− T-cells) (Strindhall et al., 2007). However, concerning individuals with a senescent immune system, a better understanding of the age-associated alterations to immunity is still necessary for helping to identify aged individuals requiring specific or additional care during or in prevention of the influenza specific season. The awareness of such changes would be vitally important for developing new type of vaccines, adjuvants and modified protocols of vaccination designed for these immunosenescent individuals.

4.3. What do we improve: the vaccine or the immune response?

As current TIV do not offer optimal protection in older adults due in part to waning cell-mediated immunity, novel vaccine designs and immunological therapeutic approaches to enhance T-cell immunity have been proposed. New formulations already tested on older individuals include increasing the TIV dosage (60 μg versus 15 μg of HA) (Cate et al., 2009; Falsey et al., 2009); changes in the type of vaccine (live attenuated vaccines (LAVs) (De Villiers et al., 2009); virosomal vaccines (Huckriede et al., 2005); and adjuvanted vaccines with MF59 or AS03) (de Bruijn et al., 2006; Peglasco et al., 2001; Roman et al., 2010; Leroux-Roels et al., 2010). Further formulation changes which are at early stages of development include enhancing adjuvantation of current vaccines (Keitel et al., 2008) or the development of novel adjuvant as the labile adjuvantation of current vaccines (Monto et al., 2009); DNA vaccines (Drape et al., 2006) and recombinant vaccines (Cox and Hollister, 2009; Treanor et al., 2007); the use of different modes of delivery the viral antigens have been assessed such as intradermal (Holland et al., 2008; Leroux-Roels et al., 2008); and alternative antigens (use of highly conserved maturational cleavage site of HA precursor, the external domain of the M2 protein, and the nucleoprotein) (Bianchi et al., 2005; Livingston et al., 2006).

In addition, it has been proposed to physically remove from the circulation and/or inducing the apoptosis of senescent CD8+ CD28− T-cells with the hope of inducing the homeostatic expansion of more functional population of memory T-cells (Effros, 2007a). Regarding the adverse impact of chronic CMV infection, a practical strategy might be the development of CMV vaccines preventively administrated during childhood (Pawelec et al., 2009). However developing such a vaccine targeting a virus as complex as CMV may not be viewed as a priority compared with vaccines against other pathogens. Different ways have also been explored how to rejuvenate the peripheral T-cell pool by reversing the thymus atrophy. Several factors including IL-7, keratinocyte growth factor and sex steroid ablation are currently taking centre stage as potential immune rejuvenators (Mitchell and Aspinall, 2009).

Current strategy bolsters the immune response by altering the microenvironment in which thymocytes develop. Treatment with recombinant IL-7 reverses thymic atrophy, increases thymic output and subsequently improves immune response of old mice and old primates (Aspinall et al., 2010). The limited studies in humans reveal also an IL-7 mediated expansion of naïve T-cells (Rosenberg et al., 2006). However, due to the interplay and regulation that exist between these different factors future strategies combining two or more of the factors which can reverse thymic atrophy will probably impart greater insight into the best way of promoting thymic rejuvenation. Other strategies such as a pharmacologic approach to enhancing telomerase are currently being addressed as possible means for the prevention or retardation of replicative senescent cells (Effros, 2007b). This follows proof-of-principle experiments demonstrating a small molecule telomerase activator (TAT2) on human CD8+ T-cells from HIV-infected donors in which positive effects have been observed (Fauci et al., 2008).

5. Conclusion

Influenza virus infection remains a major public health concern across the world and the overall body of evidence nevertheless suggests that influenza vaccination is also beneficial for aged individuals. However, this review demonstrates that the achievement of an accurate assessment of vaccine benefits is still fraught with considerable methodological and epidemiological challenges. Of course, designing new randomized placebo-controlled trials could be a solution but this would be also an expensive and an ethically complex proposition. As, more immunogenic vaccines and other strategies for enhancing protection in this high risk population have already been developed, to compare new and improved senior formulations with current formulations in head-to-head clinical trials would appear as a competitive alternative. However, there is still no gold standard against which to predict the impact of increasing age on vaccine response. Indeed, while immunosenescence is undoubtedly a real and important factor affecting vaccine response, methods for identifying and measuring it and for understanding its implications for vaccine response still require further evolution.

Conflict of interest

None is declared for this manuscript.

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