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CURRENT OPINION

Economic Evaluation of Vaccination Programmes in Older Adults and the Elderly: Important Issues and Challenges

Sevan Dirmesropian[1] · James G. Wood[1] · C. Raina MacIntyre[1] · Philippe Beutels[1,2] · Anthony T. Newall[1]

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Abstract High-income countries are undergoing demographic transitions towards populations with substantial larger proportions of older adults. Due to the increased susceptibility of older adults to infectious diseases and their consequences, vaccination programmes are an important health intervention to help maintain healthy ageing. While much of the existing literature suggests that current vaccination programmes targeted at older adults and the elderly are likely to be cost effective in high-income countries, we argue that it is important to more fully consider some important issues and challenges. Since the majority of vaccines have been developed for children, economic evaluations of vaccination programmes have consequentially tended to focus on this age group and on how to incorporate herd-immunity effects. While programmes targeted at older adults and the elderly may also induce some herd effects, there are other important challenges to consider in these economic evaluations. For example, age and time effects in relation to vaccine efficacy and duration of immunity, as well as heterogeneity between targeted individuals in terms of risk of infection, severity of disease and response to vaccination. For some pathogens, there is also the potential for interactions with childhood programmes in the form of herd-immunity effects.

✉ Anthony T. Newall
a.newall@unsw.edu.au

1 Samuels Building, School of Public Health and Community Medicine, UNSW Australia, Sydney, NSW 2052, Australia

2 Centre for Health Economics Research and Modelling Infectious Diseases (CHERMID) and Centre for the Evaluation of Vaccination (CEV), Vaccine and Infectious Disease Institute, University of Antwerp, Antwerp, Belgium

Key Points for Decision Makers

Identification of the most appropriate target/s for adult vaccination efforts involves a complex trade-off between multiple factors, including vaccine efficacy, duration of protection, and the disease burden in different groups.

Cost-effectiveness models can help to inform immunisation decisions by incorporating the heterogeneity between older individuals in these factors and other important parameters.

In some cases, herd immunity effects from childhood vaccination programmes for the same pathogen may impact on the cost effectiveness of vaccination programmes targeted at older adults, over time.

1 Introduction

There are demographic changes in many high-income countries (as defined by the World Bank [1]) that will dramatically increase the proportion (and total number) of older adults (individuals aged >50 years) and the elderly (aged >65 years) in the next decades [2]. These changes will create substantial financial and organisational challenges for healthcare systems and governments in countries around the world [3]. Based on data from the US, those aged over 65 years account for two-thirds of the total aggregate hospitalisation costs and half of all hospital stays [4].

Aging is accompanied with important physiological changes, including a decline in immune function after the age of 50 years (immunosenescence) and increasing frailty [5]. The prevalence of comorbid conditions also increases with age, and the combination of these factors results in increased incidence and severity of many infectious diseases in older populations [5]. Infectious diseases, such as pneumococcal and influenza, are substantial causes of morbidity and mortality among the elderly [6]. For instance, in the US the estimated rate of invasive pneumococcal disease (IPD) is 31 per 100,000 in those aged >65 years compared with only 2.9 per 100,000 in those aged 18–34 years [7]. Likewise, the incidence of herpes zoster increases rapidly after the age of 50 years, with a higher incidence in those aged over 80 years when compared with those aged under 50 years [8, 9].

Vaccination programmes have contributed to major reductions in many infectious diseases. While the majority of vaccines were developed to target childhood infections [10, 11], vaccination options are becoming increasingly available for older adults, including vaccines targeted at influenza, pneumococcal disease, herpes zoster, pertussis, and hepatitis A. However, even in many high-income countries, only influenza vaccine is offered free of charge to the elderly [12]. As with recent childhood vaccines, many new and emerging vaccines for adult populations are relatively expensive. For example, the 13-valent pneumococcal conjugate vaccine and live-attenuated zoster vaccine are priced upwards of $90 per dose (US price, 2015) [13]. In addition, in adults there is often a greater number of potential cohorts that could be targeted (e.g. all those aged over 65 years) compared with childhood programmes that are more often limited to a single cohort with a catch-up programme for younger children only, who are more likely to suffer from severe preventable disease (e.g. the Australian rotavirus vaccination programme only had a catch-up programme for children under 32 weeks of age [14]).

Since the majority of vaccines have been developed for children, economic evaluations of vaccination programmes have tended to focus on this age group. In the case of childhood vaccination programmes, while static analyses ignoring herd effects remain common [15] and may constitute valid, if sometimes conservative estimates, much of the methodological research has been about how to account for potential herd protection using dynamic models [16]. While programmes targeted at older adults may induce some herd effects, there are other important challenges that have received less attention. For example, the economic evaluation of programmes targeted at the elderly are often subject to important age and time effects in relation to vaccine efficacy as well as the distribution of the disease risk and comorbidities between individuals. The interaction and impact of childhood vaccination programmes on adult programmes targeted at the same pathogen is also important to consider. This article will focus on exploring these factors as they relate to the economic evaluation of vaccination programmes targeted at older adults and the elderly, and highlight other important factors that can be influential in these analyses.

Although not the focus of this article, we have also provided a brief overview of the economic evaluation literature for vaccination programmes in adults and the elderly (see Box 1). It is worth noting that most economic evaluations of vaccination programmes (for both childhood and adults) use models to estimate the impact and cost effectiveness of vaccination strategies. While the use of predictive models is often unavoidable when assessing value for money before a vaccination programme is introduced in a given setting, it is also important to examine the validity of these predictions. There have been some retrospective economic evaluations of

Box 1: A Brief Overview of Literature on the Cost Effectiveness of Vaccination Programmes for Adults and the Elderly

What the Literature Says About the Cost Effectiveness of Adult and Elderly Vaccination?

A 2013 review of cost-effectiveness analyses of adult vaccination programmes in EU countries identified 46 evaluations [17]. These included seven different vaccination programmes, with the most commonly evaluated infections being herpes zoster (11 studies), influenza (17), and IPD (10). The majority of studies used a Markov model and applied a healthcare provider (payer) perspective. They found that adult immunisation programmes were generally cost effective in high-income European countries [17]. To obtain a fuller snapshot of the literature we also examined several existing review studies that focused on specific vaccination programmes in the elderly.

A cost-effectiveness review of PPSV vaccination in adults identified 11 studies, all of which suggested that the vaccination programme was cost effective. The results were most influenced by values applied to vaccine efficacy, incidence of IPD and case mortality [18]. A review of economic evaluations of influenza vaccination among the elderly found that this programme was often cost saving [19]. In this case, the most important factors noted were the price of the vaccine and vaccine efficacy against hospitalisation and death [19]. In a systematic review of herpes zoster vaccination, all except one study concluded the programme to be cost effective, with vaccine cost, herpes zoster incidence, age at vaccination and duration of vaccine protection considered influential parameters [20].

vaccination programmes that sought to do this; however, even after implementation, there can be challenges to establishing cost effectiveness due to limitations in surveillance systems [21]. Infections can trigger medical consequences that may not be identified as being due to the infection. For instance, evidence suggests a relationship between influenza infection and acute myocardial infarction [22]. This can make it hard to establish the disease burden due to an infectious agent.

2 Heterogeneity in Older Adults and the Elderly

The term heterogeneity refers to differences between individuals and/or population subgroups in terms of their behaviour, health status and response to interventions. Demographic factors including age, sex and race, along with clinical factors and preferences (such as attitude, beliefs) could all be potential sources of heterogeneity [23]. Age itself is associated with the decline in the immune and cell repair processes that can increase susceptibility and accentuate severity of infectious diseases [10, 24]. This decline of the immune system can also differ significantly between older adults and elderly individuals (heterogeneity in immune system) as a consequence of host genetic factors and accumulation of environmental exposures (with age), including health-related behaviour such as smoking, exercise and diet [25]. While heterogeneity also exists between infants, there is greater scope for heterogeneity in the elderly. First, within the age group we define as elderly, there is a large variation in age (e.g. 65–100 years), which is closely related to disease risk through factors such as immune response. Second, even those of the same age may have considerable differences as they have had a greater time period over which to accumulate differences in relevant underlying conditions (e.g. comorbidities) and exposures that may result in a more heterogeneous risk profile within a single age group [23, 25].

There can also be heterogeneity in the immune response to vaccination in older adults (see Section 3) and in the uptake of a programme between subgroups. These differences in disease risk and vaccine efficacy, etc., between individuals can be important to consider when evaluating programmes targeted at older adults and the elderly. Economic evaluations of vaccination programmes often apply only broad age-based stratification. In some circumstances, there are likely to be benefits from implementing further heterogeneity in models, for example, stratifying by finer age categories and/or by risk groups (e.g. separating those at high/low risk within each age group); however, any stratification decision in modelling should be supported by relevant data, which may sometimes be challenging to obtain (see below).

3 Vaccine Efficacy in Older Adults and the Elderly

Efficacy is a key variable in economic evaluation of vaccination programmes (except in budget impact analysis) as it impacts the total cases prevented, which in turn affects the estimated costs and consequences of the programme. In the aging process, several aspects of the immune system decline [26]. Reduced numbers of antigen-presenting cells and impairment of cell-mediated immunity are consequences of a decline of the immune system in the elderly [27]. This change can impact vaccine efficacy in two key ways. First, it may alter the initial vaccine efficacy (shortly after vaccination) that is estimated and, second, it may alter the duration of protection from vaccination over time (waning of vaccine). An example of these effects was reported by Shapiro et al. [28] for pneumococcal polysaccharide vaccine (PPSV), where it was found that both the initial efficacy and the duration of efficacy declined as age increased (Fig. 1). This finding has also been reported for influenza vaccine, where the vaccine efficacy was lower (19 %, 95 % CI −146 to 73) in those aged >65 years compared with those aged <65 years (44 %, 95 % CI −11 to 72) [29]. The duration of the vaccine protection also appeared to decline more rapidly in those aged over 65 years, and reached zero after 120 days (waning of vaccine) [29]. Likewise, a reduction in vaccine efficacy with aging has been shown for herpes-zoster vaccination, with an efficacy estimated at 65.5 % (95 % CI 51.5–75.5) for those aged 60–69 years and 55.4 % (95 % CI 39.9–66.9) for those aged over 70 years [30]. These differences in both initial vaccine efficacy and waning of vaccine immunity have been found to be influential in the cost effectiveness of herpes-zoster vaccination programmes [31].

Immunosenescence is a process that describes the gradual decline of the immune system with age, with consequences including increased incidence of infections [32]. This process includes a range of cellular and humoral immunity defects that generally happen with aging [27, 33]. Not all components of immunity decline uniformly with increased age and there are some aspects that are preserved at the same level (e.g. CD8+ T-cell functionality) [26] or even enhanced compared with younger adults. For instance, there is evidence of increased production of pro-inflammatory cytokines by macrophages in older adults [34]. Immunosenescence in the elderly appears to be a major contributor to reduced vaccine effectiveness against infectious diseases such as IPD, herpes zoster and influenza [27, 35].

Older populations often have (multiple) chronic conditions which in turn can result in the use of multiple

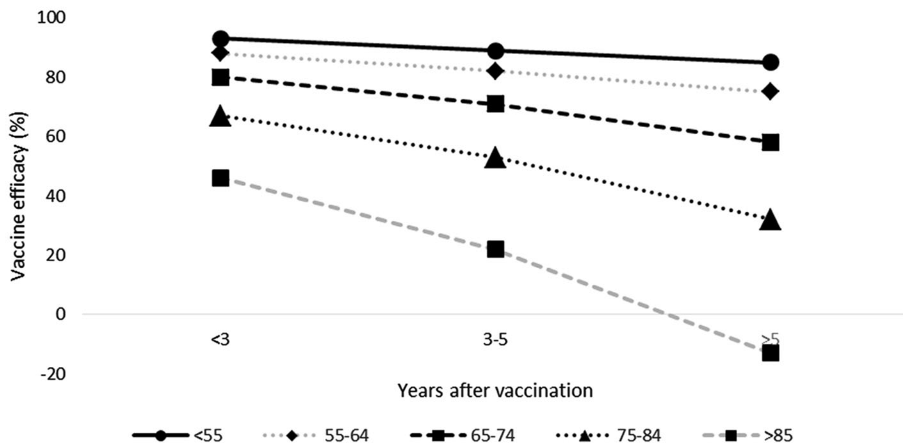

Fig. 1 PPSV efficacy and waning in different age groups. Vaccine efficacy in five different age groups (<55, 55–64, 65–74, 75–84 and >85 years) is shown for three time points (3 years, 3–5 years and >5 years) after vaccination with PPSV23. Vaccine efficacy decreases with increasing age at vaccination, and the waning of vaccine efficacy is faster in older age groups. Note the vaccine efficacy for the >85 years age group, which is negative after >5 years, is biologically implausible and indicates that the efficacy is probably close to zero after 5 years in this age group. This figure was created using data published by Shapiro et al. [28]. *PPSV* pneumococcal polysaccharide vaccine

medications (polypharmacy) [36].The presence of comorbidities can lead to increased susceptibility to infectious diseases and may also increase the severity of disease. Vaccine efficacy may also be influenced by the existence of comorbidities. For example, for PPSV it has been found that individuals with existing chronic illnesses have a poorer immune response and a lower vaccine efficacy [37]. A recent systematic review found that the prevalence of two or more comorbidities ranged from 55 to 98 % in those aged over 60 years [38]. Several lifestyle factors can also contribute to immune deficiency among the elderly, including social isolation, depression, psychological disturbance, and malnutrition [36, 39, 40]. Frailty in the elderly is another important aspect that may impact on vaccine-induced immunity and on the risk of adverse events [41]. Frailty is defined as an age-related health state where vulnerability increases due to multiple comorbid conditions, with the degree of frailty measured by a frailty index [42, 43]. It has been shown that, in addition to age difference, frailty is independently associated with limited antibody response to pneumococcal [44] and influenza vaccine [45].

Clinical trials typically exclude the least healthy individuals, including those with certain comorbidities and frail elderly [46, 47]. This reduces the available data for estimating vaccine efficacy in these groups, which can be particularly important to determining cost effectiveness due to their higher risk of serious complications from infectious disease and their potentially lower vaccine efficacy protection. Applying uniform vaccine efficacies based on clinical trials that exclude these individuals has the potential to provide overly optimistic predictions of the effectiveness and cost effectiveness of vaccination. In the absence of data from clinical trials on populations representative of those to be targeted, uncertainty analysis can be used to explore differential impacts of vaccination by health status [48]. Ideally, this should be supported by at least observational studies suggesting a difference. Some economic evaluations of vaccinations in the elderly have tried to address this issue by further stratifying ages into subgroups based on risk status and different base-case vaccine efficacies to these groups [49–51]. This practice should be encouraged where data are available to inform vaccine efficacy estimates in subgroups and where these groups also differ in either vaccine uptake and/or risk of infection and severe illness.

4 What Factors Help Determine the Optimum Age of Vaccination in Adults?

The factors discussed above tend to lead to increasing susceptibility to infectious diseases as well as disease severity with age in adult populations. At a population level, this indicates an increasing burden of morbidity and mortality with age [52, 53], which needs to be considered against generally better vaccine effectiveness in younger adult age groups. While programmes that target younger adults may create better protection compared with those targeted at the elderly [54], they may still prevent less disease overall due to the lower baseline disease burden in younger adults. In cases where vaccine immunity is long lived, the vaccination of relatively younger adult age groups may be preferable as they may be protected through to old age. Likewise, consideration must be given to the life expectancy of those to be targeted as this can impact on the time for benefits of vaccination to accrue and on the life-years gained by preventing a death in the age group targeted.

Together these factors (and others) must be traded off against each other to estimate the effectiveness and cost effectiveness of vaccinating different age groups. The potential costs and benefits of alternative strategies can be explored within an economic evaluation model. This involves a comprehensive approach to evaluation whereby multiple potential strategies are assessed and compared against each other. This process is nicely illustrated by an economic evaluation in the US that evaluated 15 different potential adult pneumococcal vaccination strategies. This involved vaccination strategies targeting different ages of vaccination (e.g. 65 or 75 years) using either a conjugate or polysaccharide vaccine, a combination of both vaccines, or no vaccination [55]. One reason this comprehensive approach is important is that an individual strategy may appear 'cost effective' when assessed against current practice but may still provide less benefit at a higher cost than a strategy not evaluated [56]. This comprehensive approach of evaluating multiple different potential age targets and assessing their relative merits has not always been applied in the existing economic evaluation literature on adult and elderly vaccination. For example, some studies have selected the use of a single potential age for vaccination (e.g. 65 years) of 13-valent pneumococcal conjugate vaccine compared with current practice [57] .

If vaccines able to provide greater initial efficacy and duration of protection in the elderly are developed, then the trade-off in the most cost effective age groups to vaccinate will also evolve. Recently, there has been increased success in the development of vaccines where effectiveness is less affected by immunosenescence (e.g. the recent inactivated zoster vaccine trial [58]). Strategies to improve vaccine efficacy may involve the addition of a suitable adjuvant to vaccines [59], changes in the route of administration (e.g. intradermal vaccination [60]) or the use of recombinant vaccines [61].

5 Vaccination Uptake in Older Adults and the Elderly

Vaccines can be recommended in adults based on different factors, including age, occupation, vaccination history, travel destinations and use of immunosuppressive drugs. However, even in universal age-based programmes, lower vaccine uptake is often observed in adults than in infant programmes [62–64]. In many countries, the systems for vaccination of adults are not as well-organised as for paediatric vaccines. In some settings it can also be more difficult to obtain accurate data on vaccination uptake in adults for use in models, as even in high-income countries, adult immunisation registries may not be available (e.g. 2009 adult vaccination survey [65]).

Several factors can influence the vaccination uptake among the elderly but a recent systematic review [66] of studies in high-income populations suggests attitudes and beliefs regarding vaccination, perceived risk and severity, vaccine characteristics (effectiveness and side effects), and healthcare provider advice were considered the most important. The role of healthcare providers is also a major factor in uptake; when asked for reasons why they did not get vaccinated, many adults cite that their doctor 'did not recommend it' [67].

One reason that vaccination uptake is important for economic evaluations is that it has implications for the financial impact of a programme. In older adults, particularly where many cohorts may be recommended for vaccination, there is the potential for large financial outlays. However, if greater uptake reduces the cost per individual vaccinated (e.g. via economies of scale), then it may still improve the cost effectiveness of the programme as benefits also increase with increased uptake. Uptake can also have implications for herd protection, although this may not be relevant for elderly vaccination programmes as it is for infant programmes (discussed below).

6 Health Sector Costs

Health sector costs include all healthcare resource use associated with implementation of the health intervention as well as costs associated with resulting changes in healthcare utilisation [56]. The vaccine price is a major determinant of the cost effectiveness of a vaccination programme. Administration costs can also be important, with improvements in cost effectiveness achieved through combination vaccines or potential provision of two or more vaccines at a single visit (e.g. PPSV and influenza vaccines).The higher rates of medical visits in older adults may provide increased opportunities for opportunistic vaccination; however, the opportunity cost of vaccine administration (i.e. for the provider's time) may still be valued, even if no additional charge is incurred.

Although the healthcare cost related to age may differ depending on the disease and setting, hospitalisation costs per event can be higher among older adults when compared with younger adults. This means that using the average cost of a hospitalisation episode for a given condition for all ages may misrepresent the healthcare cost for an older adult. For example, in Belgium, the average cost of influenza hospitalisation for all ages was estimated as approximately €2600, whereas the cost for those aged >80 years was approximately €6000 [68]. Likewise, even within the older adult population there can be substantial differences between age groups, with the estimated cost for influenza hospitalisation in those age 56–70 years (approximately €4150) being substantially lower than the cost for those aged >80 years (approximately €6000) [68]. These differences can be partially overcome by using a cost per bed-day with an age-specific length of stay; however, there may still be some differences in the cost per bed-day by age (e.g. zoster hospitalisation in the UK was estimated at £224 per day in adults aged >70 years and £195 per day in those <70 years [69]). This highlights the importance of using age-specific healthcare costs where appropriate data is available, particularly when comparing between different age-based immunisation strategies.

7 Productivity Costs

The choice in perspective can impact the cost effectiveness of vaccination programmes in older adults and the elderly, with a major issue being the inclusion of productivity costs (which will tend to favour the vaccination programme). Although other approaches are available (such as the friction cost method [70]), lost time for patients and family are often valued using the human capital approach [56]. For interventions targeting older adults, retirement ages (typically between 60 and 70 years) can strongly influence the productivity costs, depending on the age range targeted by the programme. If, for instance, the programme is targeted at people >65 years, the majority of this age group are retired and may have relatively small reductions in days of paid employment; however, other time lost by the elderly can still be considered in economic evaluation as volunteer work or leisure time has an opportunity cost associated with it [56]. Likewise, informal care of the elderly can be considered in a societal perspective [56]. Elderly individuals may also indirectly contribute to the productivity of others, with grandparent care potentially increasing the productivity in working parents [46].

8 Quality-Adjusted Life-Years

A major advantage of the quality-adjusted life-year (QALY) is that it combines both quantity gains (reduced mortality) and quality gains (morbidity reduction) from health interventions in a single measure [56]. It can also incorporate changes in utility based on age which is unrelated to changes in the health states being considered [71]. It has been argued that if health benefits of different age groups are measured based on QALYs, there would be a systematic bias that will provide priority to young people because of longer life expectancy [72]. The longer life expectancy in younger age groups means that prevention of death will naturally provide more life-years saved (Fig. 2) [73]. However, as older individuals generally have a lower quality of life, age-dependent utility weights are often

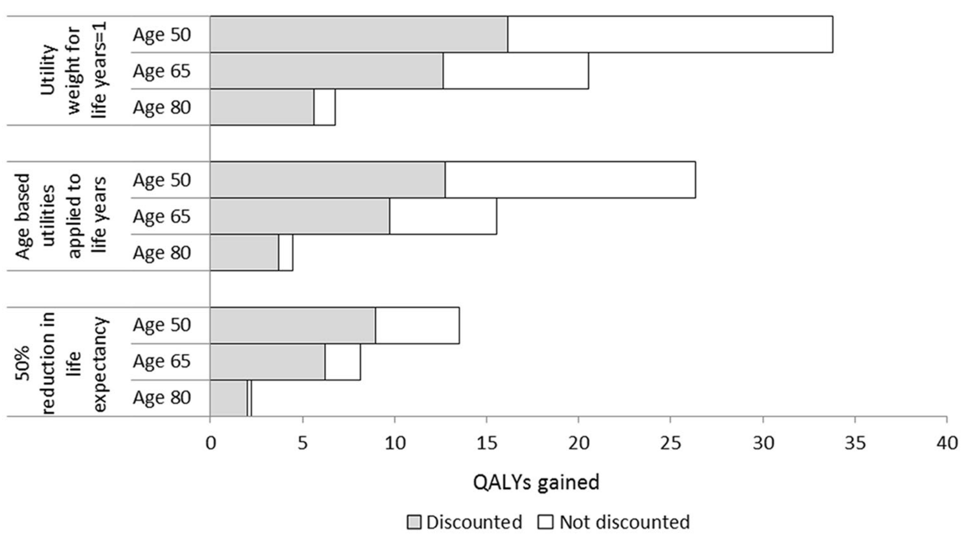

Fig. 2 Hypothetical QALYs gained by preventing death. In each section, the combined bar shows undiscounted QALYs gained and the shaded section is the discounted QALYs (5 % rate based on Australian recommendations) for three different age categories. In the top section we see results where utilities = 1 (no age utility weight effect). In this case, QALYs gained are equivalent to age-based life expectancy based on Australian population data [73]. In the middle section, age-related utility weights based on Australian data are applied [71], and in the bottom section, aged-based utility weights are applied and a 50 % lower life expectancy is applied for those who die. *QALYs* quality-adjusted life-years

applied in valuing QALYs gained [71]. In the second section of Fig. 2, when such age-based utility weights are applied [71], the QALYs from prevented mortality are substantially reduced in older adults. It may also be that those likely to die from the infection would have had a shorter life expectancy than the average individual of that age, for example, due to the higher likelihood of existing comorbidities. This is shown in the bottom section of Fig. 2, where a hypothetical 50 % shorter life expectancy was assumed for all age groups. This concept is related to that of mortality displacement, which suggests that there are some individuals in the population who are likely to die in the near future, and an event, such as an influenza epidemic, may bring forward this death by a relatively short period [74, 75].

In most situations, discounting will tend to make vaccination programmes less cost effective [76] as costs tend to occur more immediately and benefits are often delayed [77]. The impact of discounting on childhood vaccination programmes can be very influential; however, in vaccination programmes in older adults the impact is likely to be less substantial due to shorter periods between vaccination and disease prevention. Likewise, in the case of discounting of the QALYs gained from prevented mortality, the impact of discounting is less influential for older age groups (Fig. 2). This occurs because the QALYs gained from prevented mortality accrue over a shorter period (i.e. life expectancy) in older individuals.

9 The Relevance of Herd Immunity for Adult and Elderly Vaccination

Herd immunity is the term commonly used to define the indirect protection experienced by unvaccinated individuals resulting from immunisation of others in a population [78]. Although most commonly examined in universal vaccine programmes against childhood infections, herd immunity can also be an important factor in older populations. There are two potentially relevant types of herd immunity effects related to vaccination programmes in adults:

1. Potential herd protection effects offered by vaccination programmes in adults and the elderly to other age groups.
2. Herd protection from vaccination programmes of infants (children) that may interact with programmes targeted at adults and the elderly for the same pathogen

The first type of herd immunity protection (offered from elderly programmes to other age groups) has the potential to improve the cost effectiveness of vaccination programmes, but at present there is little direct evidence of substantial herd protection from elderly vaccination programmes. The main reasons for this are likely related to social contact patterns and the incidence of infection in these age groups. A survey of contact patterns in eight European countries demonstrated that the highest incidence of the initial phase of a new epidemic (transmitted by respiratory or closed contact route) will occur among school children following a secondary (lower) peak among adults [79]. This indicates that the elderly population play only a minor role in the spread of some infectious diseases, and that vaccination of the elderly will have minimum contribution to herd protection. Indeed, for some vaccines provided to adults, such as PPSV23, they may be no herd protection as they may not prevent carriage of the infection but rather reduce the rates of disease [80].

The second type of herd immunity protection that is relevant is the result of vaccination programmes targeted at children, which may indirectly protect older adults against infection. For instance, the conjugate pneumococcal vaccines have been highly effective in preventing IPD, not only in vaccinated infants but also in the wider populations, including the elderly [81]. Typically, such effects will reduce the cost effectiveness of additional programmes targeted at the same pathogen in older populations since the preventable disease burden will have decreased. However, in other examples, such as for herpes zoster vaccine, provision of the varicella vaccination to children has been predicted to reduce protective boosting of older populations, leading to a rise in the incidence of herpes zoster amongst older adults over time [82].This prediction remains controversial but, if correct, would improve the cost effectiveness of zoster vaccine programmes in older populations [69].

10 Conclusions

In the 21st century, high-income countries are undergoing demographic transition towards populations with substantially larger proportions of older adults. Vaccination programmes offer substantial scope to help protect these age groups and to help maintain positive aging. While much of the existing literature suggests that current vaccination programmes targeted at older adults and the elderly are likely to be cost effective in high-income countries, the issues and challenges we outline need to be explored in more depth. This should include greater use of individual-level data to help explore the importance of heterogeneity.

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Compliance with Ethical Standards

Potential conflicts of interest C. Raina MacIntyre has received in-kind support and funding for investigator-driven research from GlaxoSmithKline, Pfizer, Merck, and bioCSL, and has sat on advisory boards for Merck, GlaxoSmithKline and Pfizer. Sevan Dirmesropian, James G. Wood, Philippe Beutels, and Anthony T. Newall have no potential conflicts to declare.>

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