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Article *in* Expert Review of Vaccines · February 2012

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Immunosenescence and herd immunity: with an ever-increasing aging population do we need to rethink vaccine schedules?

Expert Rev. Vaccines 11(2), 167–176 (2012)

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Vaccination is a powerful public health tool that has been of tremendous benefit in protecting vulnerable populations from specific infections. Moreover, in addition to the direct benefits to vaccinated individuals, the indirect effects of protection at the community level have also been demonstrated and termed 'herd immunity'. The predicted demographic shift in the population landscape towards an ever-increasing aging population and the evidence suggesting that older individuals produce less-than-optimal vaccine responses have raised the question of rethinking vaccine schedules. This article provides evidence that even if herd immunity might be an option to indirectly protect the aging and aged adult population, the highest priorities for the near future must be to understand how vaccine responses in older individuals can be improved, to break down the public, cultural, societal and political barriers to vaccination and to counter the antivaccination movement that inhibits the worldwide spread of lifelong immunization programs.

KEYWORDS: aging • elderly • healthy aging • herd immunity • immunosenescence • vaccine effectiveness • vaccine program

World population aging: a magnitude, speed & spread never seen before

The world's population is aging steadily. The United Nations have coined the term 'demographic transition' to describe how declines in both mortality and fertility have led us to this point, which is without parallel in human history [1,201]. Over the last 50 years the number of individuals older than 65 years has tripled. By 2025–2030, projections indicate that the population aged over 65 years will be growing 3.5-times as rapidly as the total population. Europe may currently lead the world with the highest proportions of older individuals, but this may not last much longer. By 2050, nearly four-fifths of the world's older population will be living in the less-developed regions of the world [201].

The optimism created by the ever-increasing life expectancy and the expectation of many individuals that they will live longer and healthier should, however, be balanced by the reality of the healthcare burden placed on medical and social

welfare services by the increasing number of older individuals [2]. We cannot escape the simple fact that human aging is inextricably linked with an ever-increasing incidence of chronic comorbid conditions [3,4]. This is well illustrated by the progressive decline in disability-free life expectancy associated with an increase in the requirement of assisted living among older individuals in order for them to perform basic activities [5,6]. These chronic comorbid conditions may also be associated with an increase in chronic low-grade inflammation. In addition, the parallel decline in the immune system makes human aging inextricably linked with an ever-increasing susceptibility to infectious diseases [7,8].

Human aging is associated with an increasing state of susceptibility to pathogens previously encountered

Respiratory infections are common among many individuals, often producing diseases of limited duration without relapse. However, these

diseases cause a severe burden in older populations. Foremost among them is influenza, a viral infection of the respiratory tract that is often self-limiting in healthy young people but is associated with considerable morbidity and mortality in the elderly. Those over 65 years of age account for more than 90% of the deaths from influenza and are more likely to develop complications, such as pneumonia, following infection than younger individuals [9]. In the EU, between 40,000 and 220,000 deaths per year can be attributed to influenza infection, depending on the pathogenicity of the circulating viral strain [202]. The highest prevalence occurs among older adults, especially those with chronic medical conditions or immunological disorders, resulting in increased mortality [10].

Respiratory syncytial virus (RSV) also causes severe respiratory tract illnesses at the extremes of age and in immunosuppressed individuals. Repeated infection with RSV is common owing to the induction of incomplete immunity [11,12]. Although re-infections are generally mild in adults, RSV is recognized as a significant burden in the elderly. Estimates from the USA suggest that every year RSV infects up to 7% of healthy elderly adults, resulting in more than 10,000 deaths per year. In fact almost 80% of all RSV-associated mortalities occur in those over 65 years of age [13]. A study by Falsey *et al.* clearly shows that in elderly adults the presence of underlying pulmonary disease, poor functional performance status and low serum neutralizing antibody titers are risk factors for hospitalization with RSV infection [14].

Rhinoviruses are ubiquitous and are probably the most common acute respiratory viral infection, causing repeated episodes of infection throughout the life of an individual. Many physicians consider rhinoviruses to be benign and most studies underestimate rhinovirus infections [15]. In the elderly, they are, however, associated with considerable disease burden, often associated with acute exacerbations of chronic obstructive pulmonary disease [16,17], and may also contribute significantly to mortality in long-term care facilities [18].

Infection with *Streptococcus pneumoniae* is one of the main causes not only of bacterial pneumonia, but also of bacterial meningitis amongst the elderly [19–22]. Although exact figures of the incidence are difficult to establish, estimates suggest that between 12 and 48% of all cases of pneumonia are pneumococcal pneumonias [15]. Partial data collected in several European countries indicated the existence of 77,778 cases of invasive pneumococcal diseases (IPD) over the last 8 years (1999–2006) [19]. During the period 1977–2006, Cabellos *et al.* prospectively examined all community-acquired bacterial meningitis in the USA [20]. A third of the 675 cases occurred in patients 65 years of age or older and the most frequent causative microorganisms by far were *S. pneumoniae*, followed by *Neisseria meningitidis* and *Listeria monocytogenes*. *S. pneumoniae* and other causative pathogens can easily be spread from person to person through the exchange of respiratory and throat secretions, although fortunately none are as contagious as influenza.

It can be seen that the burden of influenza and pneumococcal infections remains very high. For example, in the year 2000 in England and Wales, there were 56,838 deaths from pneumonia and influenza, and of these 53,833 occurred within the proportion

of the population over the age of 75 years [23]. This is despite the fact that effective vaccines exist to fight these two pathogens, which principally concern children and adults over the age of 65 years [21].

Immunosenescence: the decline in the body's ability to mount an adequate immune response to vaccination

As depicted in FIGURE 1, older adults fail to respond properly to many antigenic stimuli compared with their younger counterparts. Therefore, vaccines are much less effective in this population [21,24–27]. Although an individual's age is a major contributor, there is no single cause for immunosenescence. Rather, it is the consequence of a compilation of events, including: thymic involution and the immune reduction in thymic output [28]; the continuous re-shaping of the immune repertoire by persistent antigenic challenge [29]; changes in APCs including the function of their Toll-like receptor ligands [9,30]; the reduced production of new B cells and the intrinsic defects arising in resident B cells [31,32]; the impact of comorbidities, the nutritional status of the individual and the increase in the frequency of low-grade and chronic inflammation [33,34]; and dysregulation of hormonal pathways [35]. This list is not complete, underlining our still poor understanding of the mechanisms and kinetics of the process that contributes to the inability of the aged body to deal with previously encountered and new pathogens [9,31,36–38]. Immunosenescence also contributes to a less-than-optimal immune response to vaccination [9,25,27,39,40], and therefore promoting immunization in the aged population does not seem to be sufficient to reduce the burden associated with vaccine-preventable diseases (VPDs) [21].

Herd immunity: when vaccinating some can protect others

As common VPDs still cause a severe burden in the older adult populations, a solution could be to consider vaccinating all younger individuals against these diseases, with the reasoning that this will limit the spread of pathogens within the community. In addition to protecting younger vaccinees themselves, this should reduce the likelihood of infection in older individuals. This is herd immunity and describes a form of 'immunity' that occurs when the vaccination of a significant portion of the population provides a measure of protection for individuals who are not vaccinated (FIGURE 2) [21,41]. The herd immunity theory proposes that in contagious diseases that are transmitted from individual to individual, such as influenza, pneumococcal pneumonia, measles, pertussis or varicella, or for which humans are an important reservoir (i.e., diphtheria), the chain of infection is likely to be disrupted when large numbers of a population are immunized [42]. This has the effect of increasing the level of population (or herd) immunity and reducing the likelihood that susceptible individuals (e.g., those who are not or incompletely vaccinated or those in whom vaccination is contraindicated or considered as less or ineffective) will be infected. The beneficial effects of herd immunity are now well documented [43–46]; however, as presented after, careful consideration should also be given to its potential deleterious effects [21,47].

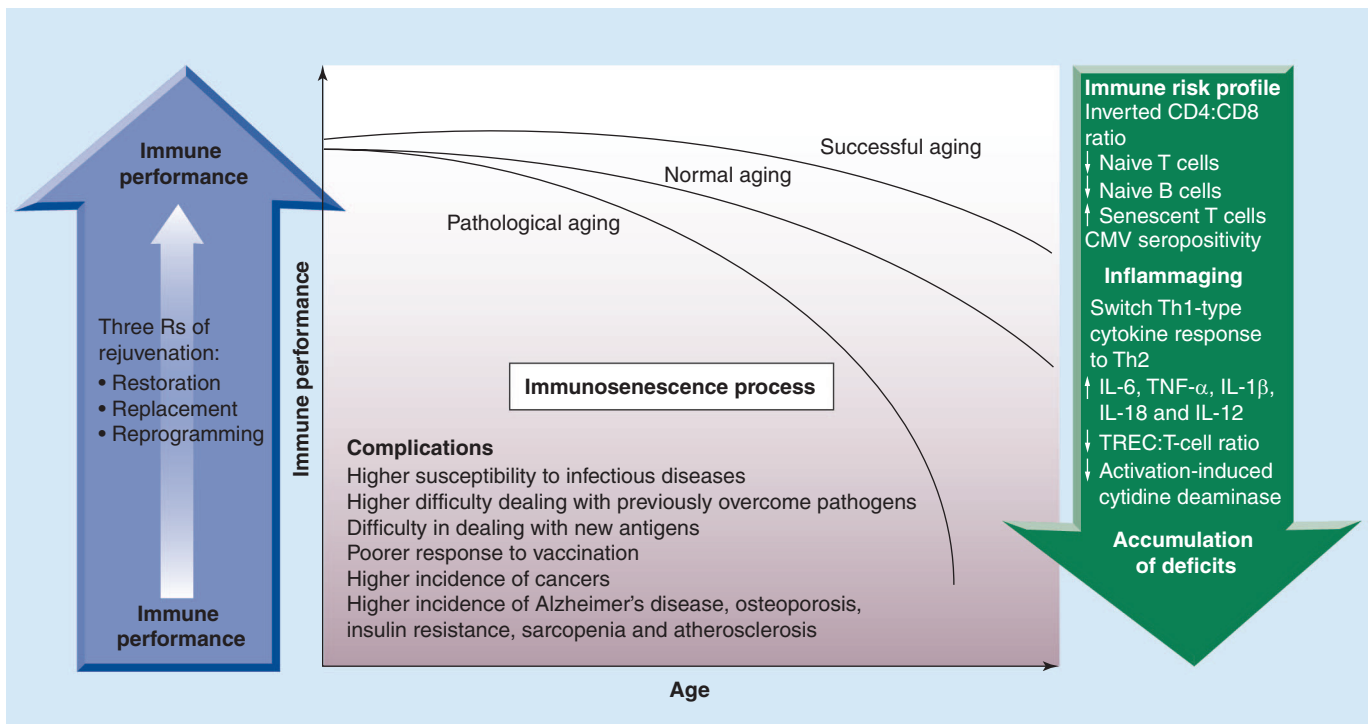


Figure 1. Development of immunosenescence with advancing age and potential beneficial impact of immunotherapy of immunosenescence (the three Rs of rejuvenation). This figure depicts the concept of accumulation of deficits applied to the development of immunosenescence. Thus, with advancing age an accumulation of immune deficits could be used to predict the immune status of a given individual and, furthermore, its aging mode (successful vs normal vs pathological aging). However, in a complex system such as the immune system, reliability of functions being undertaken is dependent in part of the quality of the component and also on any functional overlap. Thus, reliability in the face of possible component failure can be achieved by having multiple components capable of fulfilling the same task, thereby ensuring that, whilst some components fail, the system as a whole remains functional. Finally, predicting individual responsiveness to vaccination using a single and robust method able to distinguish between a healthy and immunosenescent state is still very challenging. TREC: T-cell receptor excision circles.

Herd immunity: the benefits

A quasi-experimental demonstration of the major impact of herd immunity resulted from the retrospective analysis of the Japanese experience with vaccinating schoolchildren with inactivated influenza vaccines [48]. The mandatory vaccination program initiated in 1962 significantly decreased excess mortality from seasonal influenza and IPD in all adults, including the very elderly. Subsequent relaxation of the law in 1987 and its repeal in 1994 were immediately followed by a drop in population immunization rates, an increase in deaths from influenza and IPD and an increasing trend of excess mortality in the 45–64 and 65 years or over age groups [48,49]. More recently, similar evidence came from the USA when children under 5 years of age were systematically vaccinated with the 7-valent conjugate pneumococcal vaccine (PCV7) [46]. Indeed, the use of PCV7 to help activate the T-dependent B-cell response has certainly helped to improve vaccine efficacy in infants and this is now the recommendation [50]. Thus, by reducing carriage in young children over the period 2000–2003, the initial reports of a decrease in IPD were impressive, leading to more than twice the beneficial effect of the pneumococcal vaccine itself [51]. Interestingly, this decreased incidence was also observed for IPD associated with antibiotic-resistant pneumococcal

strains [46,52]. Similarly, studies comparing long-term care facilities in which influenza vaccination to healthcare workers was either routinely offered or not, vaccine uptake was associated with a substantial decrease in mortality among patients [44].

Herd immunity: the drawbacks

One significant concern is the effect that herd immunity has on the increase in the average age of infection, especially when the severity of the disease increases with age. Thus, measles [23,36,202], pertussis [36,53–57] and diphtheria [21,36,203], which were thought of as VPDs of childhood, are increasingly being considered instead as adolescent and even adulthood diseases in populations that have not been immunized [21]. Recent epidemiological data have demonstrated a 115 and 400% increase in pertussis prevalence in the nonimmunized adolescent and adult populations, respectively [55,56], and a 68% increase in those over the age of 65 years [57]. Similarly, the number of diphtheria cases in Europe has dramatically increased, mostly among unvaccinated adolescents, the middle-aged and adults aged over 65 years [23,36,203]. Moreover, the introduction of glycoconjugate pneumococcal vaccines into carrier age groups has also been considered to be responsible for a shift in the circulating serotypes to nonvaccine serotypes [51,52,58–63]. Very

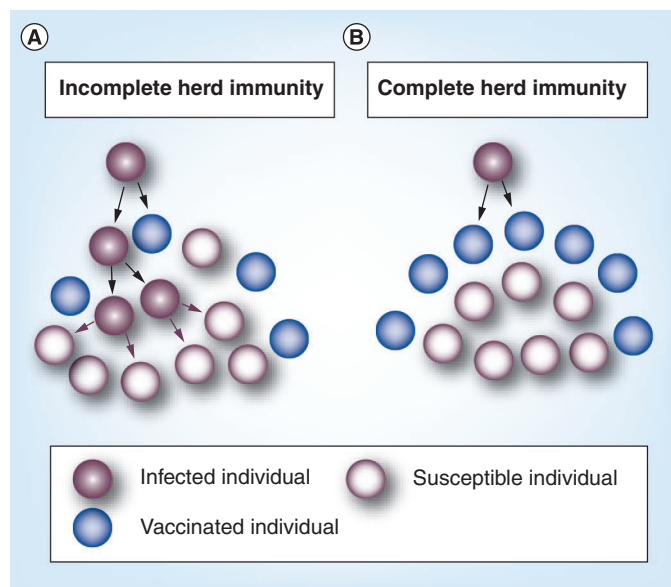


Figure 2. Schema representing the concept of herd immunity. The infectious disease considered has a basic reproductive number (R_0) equal to 2. This number corresponds to the average number an infectious person will infect with an agent in a completely susceptible population. Thus, from one infectious individual considered as the contact subject, two individuals will be infected at the first generation and four at the second (A). Therefore, the attack rate amongst susceptible individuals in the second generation is calculated as being 4/16 (25%). With a vaccine coverage rate of 50% (B), R will be equal to 1. Indeed, whether P is the proportion of immunized individuals, R is equal to $((1-P) R_0)$ and the attack rate amongst susceptible individuals at the second generation is decreased to 1/8 (12.5%). In (B), unvaccinated individuals are indirectly protected.

virulent serotypes such as 3, 7F and 19A are on the rise and multidrug antibiotic resistance among the 19A serotype isolates has become a major concern. Similarly, a recent report from the CDC showed that bacterial meningitis cases declined by 31% between 1997 and 2007 [64]. The drop was led by reductions in infections by *N. meningitidis* and *S. pneumoniae* that are covered by available and effective childhood immunization programs. But with fewer infections among young children, the burden of the disease is now mainly borne by older adults. Particular attention could also be given to herpes zoster [21]. With mass vaccination of infants, the overall incidence and morbidity of varicella would probably be reduced [65]. However, as demonstrated by Bonmarin *et al.*, whatever the vaccine coverage and the vaccine policy used, vaccination could not only be associated with a shift in age distribution of varicella but mainly with an increased incidence of herpes zoster among older adults [65]. Indeed, it has been well demonstrated that subclinical varicella zoster virus infections could last a lifespan, thus providing a boosting effect to specific cell-mediated immunity. This could thereby contribute to a reduction in the spread of virus throughout the population [66,67].

Finally, the current attitudes towards vaccination in most industrialized countries have led to considerable success of childhood vaccination schedules, but also to fundamental changes in

the epidemiology of the common VPDs [21,23]. While it is widely believed that current immunization strategies save many lives, VPDs still place a considerable burden not only on older adults but also on the adult population and healthcare systems of most developed countries [7,8,68–72]. In the USA, where approximately 100–300 children die annually of VPDs, aside from a 350-fold increased likelihood of death, VPDs are also associated with an age-related increase in serious adverse health outcomes, leading to hospitalization, antibiotic misuse, debilitating complications and/or death [69,73]. While historically, vaccines were deemed to be ‘just for children’, vaccines for adults are becoming increasingly common and necessary [74]. However, most adults only think of the tetanus booster recommended every 10 years and even then, many adults only get the vaccine if they injure themselves [75]. Unlike childhood vaccines, which are often required for entrance to schools, adult vaccines are not mandated. No requirements and a lack of preventive healthcare by most adults have led to low levels of vaccine use by adults [73,74]. Thus, while there is a certain truth to the statement that a good adult immunization program begins with a good childhood vaccine schedule, these findings must make us shift our thinking and efforts away from predominantly childhood-centered immunization schedules toward a more balanced approach across the lifespan [21,73].

Is herd immunity a sustainable approach in a world that is more closely networked than ever before?

The importance of maintaining high vaccination coverage rates in children and optimizing vaccine and booster dose uptake during adulthood is well known [23,36,76], not only for its direct benefit to the vaccine recipients, but also for its indirect effects. However, one major flaw in the argument that herd immunity would be a beneficial option to take in order to limit the burden of VPDs in the elderly is that aged individuals should then be strained to remain in closed contact with vaccinated populations. But this is not the reality. Individuals now travel more than either their grandparents or parents. The world is now more closely networked than ever before and the increased amount of air travel means that the spread of any pathogen across the globe can occur within hours, as was well observed with recent H5N1 and H1N1 pandemics [77]. This is also demonstrated by the emergence of over 300 infectious diseases in the human population since 1940, enlarging the spectrum of pathogens encountered [78]. Evidence for a shift in the infectious agents affecting individuals in Europe comes from studies on vector-borne infections, such as West Nile virus, dengue fever, malaria and chikungunya, which were considered to be largely absent as endogenous diseases in continental Europe [79]. These have made a return in recent years, both in Europe and the USA. One complementary and interesting point was also related to the usual age range of the individuals affected. During the first outbreak of West Nile virus in the USA in 1999, the median age was 71 years, with 73% aged over 60 years [80]; in Israel in 2000, all of the victims were more than 78 years of age [81].

The elderly are increasingly part of this trend, and while little data exist on the demographic profile of current air passengers, a report to the House of Lords (UK) indicated that 10% of passengers were over 65 years of age. Thus, the number of older people passing through UK airports in recent years may be in excess of 24 million [204]. Although it is likely that many of these are repeat flyers who go abroad two or three times a year, as documented by recent studies, this would lead to a conclusion that between 8 and 12 million people over the age of 65 years were air passengers from UK airports [205]. If only half of these were people whose journey originated in the UK, it would suggest that between 30 and 50% of the population over the age of 65 years in the UK flew once a year.

By traveling so much, older adults are thus more likely to come into contact not only with uncommon but also common pathogens. Indeed, across the world, including in developed countries, the vaccine coverage rates observed for the most common VPDs are far from uniform. In fact, they are often below the WHO recommendations [82]. While the number of diphtheria cases has dramatically increased within Europe and mostly concerned unvaccinated adolescents, middle-aged adults and people over the age of 65 [23]; in the USA only 2% of adults aged 18–64 years are vaccinated with the tetanus and diphtheria toxoids combined with acellular pertussis vaccine [206]. The coverage rates concerning 23-valent pneumococcal polysaccharide vaccine administration among high-risk adults aged 19–64 years range from 9 to 21% in Europe [83] and were estimated at 17.5% in the USA [206]. Similarly, influenza vaccine coverage rates vary considerably across Europe (i.e., from 25 to >70%), and only two European countries are close to reaching the WHO objective of 75% [83].

Moreover, and independently of the coverage rates, vaccines are not uniformly effective and elicit variable specific immune responses across the world depending on environmental factors and host genetic factor, as well as the age of the recipient [84,85]. Some vaccines, such as measles, mumps, rubella, hepatitis B and others, fail to induce lifelong protective levels of antibodies in approximately 5 to 10% of healthy recipients. This results in the inability to protect against infectious diseases and the accumulation of vaccine failures, resulting in eventual outbreaks [84,86]. So even if a sufficient proportion of the population were to be vaccinated to reach the herd immunity threshold, the one-size-fits-all approach for vaccination may not be sustainable in the prevention of common VPDs across the world [77].

Expert commentary

While VPDs still remain a major global public health concern for the adult population worldwide [69], most industrialized countries consider childhood immunization programs as a priority. Childhood vaccine programs around much of the world have been a success, with childhood deaths due to VPDs decreasing by as much as 95–99% [21,87]. Such success has bred complacency and the global vaccine coverage rates for most common VPDs are now lower than recommended [19]. This shows that many have forgotten the long history of stunning triumphs of vaccination programs, only to focus their current beliefs and attitudes on

incomplete or biased knowledge [23]. The world has become more closely networked than ever before, not only by the burgeoning of air travel, but also through the internet, social networking services and blogging, and this has increased the spread of information as well as misinformation [77]. Public health has, thus, become more vulnerable to vaccination protest movements, which have contributed to a reduced public acceptance of vaccines [74] and the development, often for erroneous reasons, of strange and illegal behaviors [88,206,207]. In 1998, the claim that the MMR vaccine plays a causative role in autism created a worldwide controversy [89] and led to a decrease in its use in many countries [71]. The results have been heartbreaking. Since 2006, Switzerland has experienced measles outbreaks in which there were more than 3577 cases in 21 of 36 counties, one death and 260 hospitalizations, of which 147 were for pneumonia and eight were for encephalitis [203]. In total, 20% of cases were 20 years of age or over; 93% were only partially vaccinated or unvaccinated. This was largely attributed to low vaccination rates, and currently only 71% of children 2 years of age are vaccinated with the recommended two doses of MMR vaccine and 87% only with one dose [203]. As of 18 April 2011, 33 countries in Europe had reported 6500 measles cases. In addition, in 2011, there were outbreaks and an increase in the number of cases reported in Germany, The Netherlands, Norway, Romania, the Russian Federation, Switzerland and the UK [90]. Similar figures can be drawn for pertussis within countries where routine pertussis vaccination was dropped in the 1970s and 1980s [71]. Recently, the H1N1 pandemic revealed the strong public fear of vaccination stoked by antivaccinationist groups. In the USA, 70 million doses were wasted, although there was no evidence of harm from the vaccine [71]. Finally, in the WHO European region, 500,000 infants do not receive full protective immunization and 32,000 die each year from VPDs [74]. Even more recently, a growing number of parents are scheduling varicella and influenza playdates (e.g., pox and flu parties) where children share lollipops, and trade germ-infected pajamas and other infected items with people who claim to have infected children to spread the disease and avoid vaccinations [207,208]. The parents use social networking services to make contact with these strangers. The unknown person then mails the potentially infectious matter to the requester, who gives it or feeds it to his or her child in the hope that the child will become ill. However, not only will these methods probably not transmit the disease effectively or reliably, because the pathogen usually cannot survive for very long on the surface of such items, but it may also be a reliable method of transmitting other infections, including hepatitis B, group A streptococcal infection and staphylococcal infections that are potentially deadly diseases that the parents never intended to expose their children to [91].

Together, these findings demonstrate that the current attitude towards vaccination programs have led to fundamental changes in the epidemiology of common VPDs across the different age strata. They also reflect a number of underlying healthcare, economic, cultural and/or political beliefs [70] that will render difficult any efforts towards shifting the focus of vaccine programs from childhood toward a lifelong immunization

program [21,23,47,70]. Indeed, the shifting of vaccine targets from the poorer responders to groups with little direct benefit but better immune responsiveness to vaccines represents a considerable societal challenge in view of the tension between individual rights and public health [92].

In taking this approach towards improving the uptake of vaccines and ensuring their success in the eradication of disease, we need to consider their use as agents of protection irrespective of the age of the recipient. A common belief, currently being reassessed, is that vaccine efficacy is independent of age, such that a vaccine against, for example, influenza should invoke protection in children, adolescents, adults and the elderly. Much recent work has shown that the ability of a vaccine to provide adequate protection roughly depends on recipient age. Thus, influenza vaccination leads to protection in more than 70% of younger individuals, but is ineffective in half of the elderly population [9,36]. Similarly, vaccination against hepatitis B provides suboptimal responses in the elderly. Following a review of the available evidence in March 2011, the Joint Committee on Vaccination and Immunisation issued a statement on the routine pneumococcal vaccination program for those aged 65 years and older, advising that it be discontinued, with the vaccine continuing to be offered to those aged 65 years and over in clinical risk groups, based on clinical judgment [209]. In order to establish greater confidence in vaccine programs it is now time to design better vaccines, because the effectiveness and safety of the vaccine are the strongest predictors of vaccine uptake [74].

Five-year view

The combination of the world population aging at the current rate, the decreased efficacy of vaccines in the elderly and the fear of an influenza pandemic has prompted an increased degree of interest in developing more immunogenic vaccines and vaccines capable of conferring lifelong protection [9,77,93]. Although better vaccine formulations have been proposed, controversy has raged over what is the best method to use to improve these vaccines. One approach has been to consider alternate routes of immunization, such as the intradermal or intranasal routes [94]. Another has been to assume that the immune response will become gradually weaker with age and so requires a stronger stimulus, such as higher vaccine dose [95] and/or new adjuvants (e.g., MF59 or AS03) [96]. This may achieve success, but it could be short-lived, possibly only delaying the problems associated with older individuals for a few years. Many older adults who received these strong stimuli earlier would need even stronger later ones because their peripheral T-cell pool would then be composed of much fewer naive cells and a burgeoning number of senescent T cells [9,97,98]. Thus, in order to enhance the ability of a decaying immune system to respond to vaccination, future research perspectives should be to define the problems and fix them. Some indicators are already being studied. For example,

the activation-induced cytidine deaminase level in influenza-stimulated B cells correlates with the serum antibody response [99], and the number of signal joint T-cell receptor excision circles (sj-TRECs) per T cell (TREC ratio) could be considered as a marker of the resting naive T-cell pool [100–102] and/or a predictive marker of the vaccine response [103].

Paradoxically, however, the global success of mass immunization strategies contrasts with the largely recognized failure of strategies targeting individuals at increased risk of complications, whether from underlying disease or treatment. Moreover, such a move from the existing immunization menu towards ‘à la carte’ vaccination would probably be restricted to a few novel expensive vaccines with potentially higher efficacy but with a possibly higher risk of adverse events [70]. However, recent advances in a number of molecular profiling technologies, including proteomic profiling, metabolic analysis and genetic testing, could allow a greater degree of personalized medicine in the near future than is currently available [84]. This would certainly contribute to: accelerating the development of new vaccines with higher efficacy and conferring lifelong protection without the need for booster doses; vaccines with fewer side effects and enhanced safety that would also increase their acceptability; identifying molecules and signaling mechanism include in the induction and persistence of effective immune memory; and finally to addressing whether it is possible to rejuvenate the immune system and to limit the adverse impact of comorbid conditions on immunity. However, given the complexity of the immunosenescent process and the lack of an operational definition, we will not yet be able, within the next 5 years, to develop validated assays using strong biomarkers to predict an individual’s immune capacity and ability to respond to vaccination. This could also be used to identify those who could benefit from rejuvenating technologies, which has been achieved in experimental systems, but has yet to be transferred to the clinic (FIGURE 1) [104].

Thus, the highest priority for the near future must be to understand and break down the public, cultural, societal and political barriers to vaccination and counter the antivaccination movement, which together inhibit the worldwide spread of vaccination in all age groups. This should be done before we rethink life-course vaccine schedules and use super-effective and newly designed vaccines.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Common vaccine-preventable infectious diseases still cause a severe burden in the aging and older adult populations.
- Current attitudes towards vaccination in most industrialized countries have led to fundamental changes in the epidemiology of these common vaccine-preventable infectious diseases that further increase this burden.
- While promoting lifelong vaccine programs in order to reach the herd immunity threshold at the community level could be an attractive option to indirectly protect the vulnerable part of the adult population, shifting the emphasis away from a predominantly childhood-centered vaccine program toward a more balanced approach across the lifespan is, however, confronted with underlying healthcare, economic, cultural and/or political barriers.
- In addition to understanding and breaking down the public, cultural, societal and political barriers to vaccination, we must assume that the immune response becomes gradually weaker with age.
- Recent advances in a number of molecular profiling technologies, including proteomic profiling, metabolic analysis and genetic testing, contribute to the improvement of vaccines or/and the enhancement of the abilities of the immune system by:
 - Enabling the development of vaccines with higher efficacy and conferring lifelong protection without the need for booster doses;
 - Enabling the development of vaccines with fewer side effects and enhanced safety, which would also increase their acceptability;
 - Identifying molecules and signaling mechanisms involved in the induction and persistence of effective immune memory;
 - Addressing whether it is finally possible to rejuvenate the immune system and to limit the adverse impact of comorbid conditions on immunity.

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