

Balancing the Efficacy and Safety of Vaccines in the Elderly

Ian J. Amanna*

Najit Technologies, Inc. 505 NW 185th Avenue Beaverton, OR 97006, USA

Abstract: With advances in global health care, ageing populations are expected to grow worldwide throughout the 21st century. Increased lifespan is a testament to modern medical and social practices, but also presents a growing challenge to a system with limited resources. Elderly populations present specific concerns related to preventative health practices, especially vaccination. Although the power of vaccination is unquestionable in controlling infectious disease, immunosenescence can lead to reduced immune responses following immunization in the elderly, and increased morbidity and mortality. Further complicating this issue, some vaccines themselves may pose a substantial safety risk in the elderly when compared to younger counterparts. Though any health care intervention must balance risk and reward, safety and immunogenicity are often poorly characterized in older populations. This review explores several domestic and travel vaccines, examining what is known concerning efficacy and safety in the elderly, and considers future alternatives.

Keywords: Vaccines, ageing, immunity, immunosenescence.

THE CHALLENGE OF VACCINATING AN AGEING POPULATION

In our era of modern health and hygiene practices, one major outcome has been an increase in life expectancy. The United Nations reports that global life expectancy has increased from an average of 58 years in 1970-75 to 68 years in 2005-2010 [1]. This trend is expected to continue, with the average global lifespan increasing to 76 years by 2050. These projections indicate that the global population considered to be elderly (≥ 60 years of age) will see a dramatic shift from current levels of 11%, to up to 22% of total population by 2050 [1]. In North American and European countries, populations are predicted to see an unprecedented rise in the elderly with projections that over 30% of the population will be >60 years of age by 2050 [2].

Though increased life expectancy clearly points to the success of improved health practices and social systems worldwide, it presents a growing problem from the standpoint of infectious disease control and prevention. In general, elderly adults are at increased risk for disease morbidity and mortality when compared to their younger counterparts [3]. This is most strikingly illustrated by age-specific mortality rates associated with influenza/pneumonia [4]. At the turn of the century in the United States, influenza/pneumonia placed a significant morbidity and mortality burden on both the very young and the very old, giving rise to the canonical “U-shaped” mortality curve shown in Fig. (1a). While a slow but steady rise in mortality could be seen throughout adulthood, a dramatic rise occurred from age 65 onward. Unfortunately, though influenza/pneumonia mortality rates have improved for all age groups in the U.S., this disease continues to disproportionately affect the elderly. From 1911-1915, the age-specific death rate for people >85 from influenza/pneumonia

averaged $\sim 2,500$ per 100,000 (calculated from Tables 5 and 6 in [5]). From 1999-2007 this death rate in the same population averaged about 600 (page 30 in [4]), an approximate 4-fold decrease. By comparison, infants under one year of age saw over a 200-fold decrease in influenza/pneumonia-specific death rates during the same time frame (Fig. 1a).

High morbidity and mortality rates associated with disease in the elderly are common across a spectrum of pathogens. Measles, once a universal childhood disease in the pre-vaccine era, could devastate populations upon first encounter [6]. Although Panum demonstrated over 160 years ago that childhood immunity against measles could extend into old age [7], the effects of disease in elderly naïve populations could be severe [8]. During one well-documented epidemic in southern Greenland in 1951, of the 48 deaths associated with measles, greater than 60% occurred in those over 55 years of age, even though only 7% of total measles cases occurred in this age group [9]. Similarly, while immunity following smallpox vaccination in childhood and early adulthood appears to be well maintained over time [10-13], outbreaks on virgin soil could decimate populations across age groups [14]. These examples help to illustrate the particular risk that primary infections pose for the elderly, and underscore the need for improved vaccination strategies against *de novo* antigens in this age group.

While our era of modern vaccine technologies has witnessed significant progress in preventing infectious disease in the young, the elderly remain at elevated risk for many recurrent diseases. A current list of U.S. vaccines available for the elderly is presented in Table 1, including vaccines against common illnesses such as influenza, pneumococcal infections, tetanus, diphtheria, pertussis and herpes zoster (shingles). Nevertheless, immunogenicity and safety remain key questions, with specific studies in the elderly often limited. An additional concern is the expanding travel market. Reports have shown that up to 13% of the estimated 1 million U.S. citizens that travel abroad each year to developing

*Address correspondence to this author at the Najit Technologies, Inc. 505 NW 185th Avenue Beaverton, OR 97006, USA; Tel: 503-466-3895; Fax: 503-466-3896; Email: iamanna@najitech.com

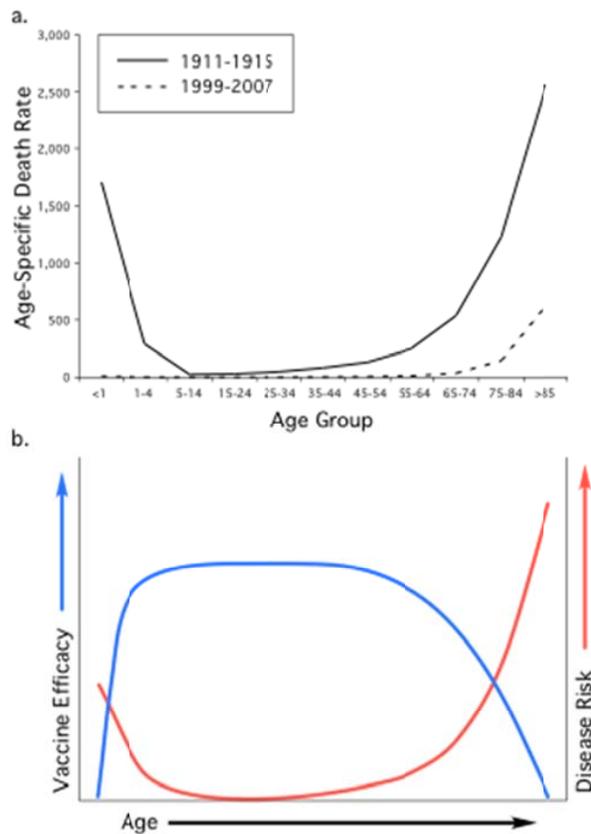


Fig. (1). The dilemma of increased risk and decreased efficacy in the elderly. a) Shown are the age-specific annual death rates for different age groups due to influenza/pneumonia. Death rates are calculated per 100,000 people in each age category. The curve for 1911-1915 was derived from Tables 5 and 6 in [5]. Average data from 1999-2007 was calculated from Table 9 in [4]. b) A conceptual graph demonstrating the drop in vaccine efficacy to *de novo* antigens in contrast to the increase in disease risk during ageing, leading to a vulnerable population in the elderly.

countries are ≥ 65 years of age [15]. For the elderly, these trips are primarily for leisure, and given projected increases in the U.S. population over the next half-century, it is reasonable to assume the numbers of elderly traveling abroad will continue to rise. Travel to the developing world puts the elderly at risk for many diseases, including vaccine-preventable illnesses such as typhoid, rabies, Japanese encephalitis virus and yellow fever. However, despite the availability of vaccines for seniors in this travel demographic, little is known regarding safety and efficacy in the elderly. Health providers, who must weigh the protective benefits of immunization with the increased safety risks often observed in the elderly, have only limited information in many instances. Only through well-informed decisions that carefully balance safety and efficacy can the healthcare community effectively protect this population.

INFLUENZA VACCINATION IN THE ELDERLY

Why are the aged at such an increased risk for infectious disease? One principal hypothesis is that the elderly respond poorly to vaccines as a manifestation of immunosenescence

[16-18], leaving them less protected following exposure to pathogens. The term immunosenescence covers a wide range of characteristic changes to the immune system during the progression into old age. Effects can be observed both in the innate immune system, such as reduced phagocytic activity by neutrophils and macrophages, as well as strikes to adaptive immunity, including reduced thymic output of T cells and diminished antibody responses to new antigens [17]. An area of intense interest examining the intersection of ageing and immunity has been the influenza vaccine.

Although the CDC recommends annual influenza immunizations for all persons over the age of 6 months, including the elderly [19], conflicting studies in older populations have suggested a range of protective effects following vaccination, from an astonishing reduction of 50% for all winter mortalities [20] to much more limited benefits seen in other observational studies [21, 22]. This variability has called into question the level of benefit associated with influenza vaccination in the elderly, with some groups specifically asking if a “healthy-user” effect underlies the bulk of the observed advantage. In particular, several studies have examined the protective effect associated with influenza vaccine outside of the standard flu season. In one observational study, Eurich et. al. demonstrated a statistically significant ($P = 0.004$) 51% reduction in mortality for vaccinees ≥ 65 years old outside of the influenza season [23]. Yet this effect was dramatically reduced following adjustment for confounders such as functional and economic status (19% reduction, $P = 0.61$). In a similar study, Jackson and coworkers looked at the relative risk of all cause mortality in seniors before, during and after influenza season over the course of eight years [24]. In all instances the vaccinated group demonstrated a significant protective advantage regardless of timing, with the bias prior to influenza season able to account for the protective effect observed during active flu season. However, the authors go on to note that using protection from mortality alone may be too broad of a measure to best estimate the health benefits associated with influenza vaccination, considering that influenza infection is estimated to account for only $\sim 10\%$ of all death during influenza season.

While the absolute level of direct health benefits from influenza vaccination in the elderly remains uncertain, the picture of the influenza-specific humoral response in the elderly is becoming clearer. One recent meta-analysis examined 31 influenza vaccination studies performed from 1986 to 2002 [25]. In this particular report, the ‘young’ ranged from 17-59 years, while the ‘elderly’ ranged from 58-104 years. Pre-vaccination, both groups looked surprisingly similar in terms of those considered protected (hemagglutinin inhibition serum antibody titers >40) and absolute geometric mean titers. Nonetheless, in an unadjusted comparison of the groups post-vaccination, younger adults consistently outpaced elderly subjects. When adjusted for a series of possible confounding factors (health status, vaccination prior to study, living situation, type of vaccine, etc.) these differences were amplified, with younger adults demonstrating a 2-4-fold better response than the elderly. Further, when examining the ‘young elderly’ (65-75 years) to the ‘very elderly’ (>75 years), the young elderly generally outperformed the very elderly, suggesting a continuum of reduced responses as a function of age (Fig. 1b). Based on these antibody respons-

Table 1. Vaccines Currently Available for the Elderly in the U.S. (≥ 65 Years of Age)^a

Vaccine	Recommendation	Vaccine Type	Efficacy Studies in the Elderly ^b	References
Influenza ^c	1 dose annually	Inactivated	+	[25, 27, 45]
Pneumococcal (PPSV)	Once at age ≥ 65 years	Polysaccharide	+	[88, 89]
Zoster	Once at age ≥ 60 years	Live attenuated	+	[59]
Tetanus, diphtheria (Td)	1 dose every 10 years	Protein	+/-	[90-92]
Meningococcal ^d	High-risk ^e	Polysaccharide	+/-	[93, 94]
Measles, mumps, rubella	High-risk ^e	Live attenuated	-	NA
Hepatitis B	High-risk ^e	Protein	+	[95]
Hepatitis A	Travel ^f /High-risk ^e	Inactivated	+/-	[69]
Typhoid	Travel ^f	Polysaccharide/live attenuated	-	NA
Polio	Travel ^f	Inactivated	-	NA
Rabies	Travel ^f	Inactivated	+	[74, 75]
Japanese encephalitis	Travel ^f	Inactivated	+/-	[73]
Yellow fever	Travel ^f	Live attenuated	-	NA

^a Adapted from [16] and [19] with modifications.

^b +, performed specifically in the elderly; +/-, elderly included in study; -, information unavailable for the elderly

^c Adults over the age of 65 may receive the standard inactivated influenza vaccine, or the high-dose vaccine (Fluzone).

^d The meningococcal polysaccharide vaccine (MPSV4) is preferred for those ≥56 years of age.

^e High-risk may include factors based on medical, occupational, and lifestyle indications.

^f Travel to areas with endemic infection and high-risk of exposure.

es the authors estimated a clinical vaccine efficacy of only 17-53% in the elderly, as compared to the CDC estimate of 70-90% in young adults [26]. This estimate for the elderly matches well with one of the few randomized double-blinded placebo-controlled trials carried out in this age group [27]. In this study, investigators found that elderly subjects (≥60 years) demonstrated a risk reduction of 58% from serologically confirmed clinical influenza following vaccination. However, following age-stratification, the protective effect appeared substantially reduced for those over 70 years, again pointing to further decreases in efficacy for the very elderly.

HOW TO BOOST THE INFLUENZA RESPONSE WITH ADVANCED AGE?

Considering the reduced vaccine efficacy observed in the elderly, can the immune response in this at-risk group be enhanced? A common response to the basic question of vaccine efficacy is often to advocate for the use of live attenuated vaccines. However, debate still persists regarding the relative merits of inactivated and live vaccines [28]. While many consider live vaccines, by their very nature, superior to inactivated vaccines, inactivated vaccines play a substantial and vital role in achieving public health immunization goals. In addition, live viral infections may pose an increased risk for systemic adverse events, and should be considered with some caution in elderly individuals.

For influenza vaccination, both inactivated and live attenuated (FluMist™) vaccine formulations are licensed for use in the U.S. [19]. The current live attenuated vaccine (LAIV) is comprised of three season-matched influenza

strains (typically two type A and one type B), which have been attenuated through cold-adaptation to allow growth in the nasopharyngeal tissues but not the deeper lung tissues [29]. Similarly, the trivalent inactivated influenza vaccine (TIV) is typically made from three circulating influenza strains that have been purified and inactivated by various chemical methods. How well do these vaccine types perform in head-to-head comparisons? In children, the live attenuated vaccine appears efficacious, with up to 90% prevention against culture-confirmed influenza [30], and it may hold an advantage over inactivated formulations in this age group [31]. However, this advantage can diminish with age [32]. Recently, a blinded, placebo-controlled randomized study carried out in healthy adults (18-49 years of age) during the 2007-2008 flu season directly addressed this question [33]. Researchers found that the TIV demonstrated a 72% efficacy in preventing laboratory confirmed influenza A. By comparison, the LAIV was only 29% efficacious, with TIV estimated to have outperformed the LAIV by 60%. Although speculative, the authors point out that the inability of LAIV to effectively boost some adults might relate to pre-existing immunity following past exposures to similar strains of influenza, which could explain the dramatic loss in efficacy of the LAIV with age [32], and be cause for concern in the elderly.

In elderly individuals, only limited studies are available that directly compare live and inactivated formulations. In one placebo-controlled study investigating the use of LAIV in the elderly, the authors demonstrated 42% efficacy in protecting against culture-confirmed influenza [34]. In two separate studies examining TIV in a similar age group, researchers found a 58-65% reduction in serologically con-

firmed clinical influenza [27, 35]. This suggests an advantage of the TIV over LAIV in the elderly, in line with trends observed in older adults [32]. However, these were separate studies carried out in distinct geographical locations during different flu seasons. To better understand the relative efficacies of the vaccine types in the elderly requires a direct comparison in the same study population. To date there is one published report of a randomized controlled study directly comparing live versus inactivated influenza vaccine in the elderly (≥ 60 years old) [32]. In terms of seroconversion, LAIV only demonstrated rates of 3-20% against influenza (A and B strains), while TIV showed much higher rates of 49-65%. For disease prevention, LAIV was 42% efficacious in preventing culture-confirmed influenza, while TIV demonstrated 50% efficacy. Though the low incidence of influenza limited the conclusions of the study, the authors estimated that the relative efficacy of LAIV was only half that observed with TIV in the elderly. In total, current studies point to a decrease in efficacy for the LAIV as people age [32], suggesting that live attenuated vaccines do not necessarily outperform inactivated vaccines in terms of protection against disease. Paradoxically, as seen in healthy adults poor responses to LAIV in the elderly may be driven more by pre-existing immunity to similar strains of virus rather than immunosenescence, signifying the need for alternative vaccination strategies in this at-risk age group.

In addition to concerns over efficacy, researchers must also address the safety of a live attenuated vaccine in an older population. Studies of early live attenuated influenza vaccines in all age groups (1-65 years) showed elevated risk for systemic reactions when compared to placebo, including sore throat, runny nose, lethargy, headache and muscle ache [36]. Although the reported reactions were relatively mild, preliminary studies in the elderly suggested an increased risk for respiratory symptoms (nose and throat irritation) [37]. These initial reports have been recently confirmed with a large placebo-controlled trial in South Africa, which demonstrated a wide range of reactogenicity events in the immunized elderly including fever, muscle ache, headache and various respiratory symptoms [34]. In fact, the manufacturer cites concerns over safety and limited efficacy in older age groups as reasons why LAIV is contraindicated for persons over the age of 50 [29], consistent with current CDC recommendations [19].

If live vaccination is not the answer in the elderly, what other options are available? In European countries, an adjuvanted influenza vaccine (Fluad®) using the squalene-based MF59 adjuvant has been approved for use since 1997, but is not currently licensed in the U.S. [38]. While several studies have been published indicating increased immunogenicity in the elderly [39, 40], as noted elsewhere few field studies specifically addressing vaccine effectiveness are available [41]. One recent FDA-approved alternative is the use of a high dose TIV (Fluzone® High-Dose, Sanofi-Pasteur) specifically for adults aged ≥ 65 years [42, 43]. The standard TIV dose contains 45 μg of inactivated vaccine antigen (15 μg of each of the three recommended strains). The newly licensed high-dose vaccine contains four times that amount, with 180 μg of total antigen (60 μg of each strain) [44]. Currently, the relative efficacy of the high-dose formulation versus the standard dose is unknown, with a 3-

year post-licensure study due for completion in 2012 [42]. However, initial studies examining immunogenicity show a clear advantage for higher doses in the elderly [45-47]. In one double-blinded placebo controlled study carried out in persons ≥ 65 years of age, the high-dose formulation gave both higher seroconversion rates, as well as increasing antibody titers up to 80% when compared to the standard dose [45]. This trend was maintained even into the 'very elderly' age group (≥ 75 years), who are at particular risk for complications from influenza. Although rates of injection site reactogenicity were more common with the high-dose formulation, the overall rates of systemic complaints were comparable to the standard dose. Given the advantage of high-dose vaccine formulations in eliciting serum antibody responses, and the risks associated with disease in the elderly, a limited increase in injection site pain may be an acceptable balance for enhanced protection.

CONTINUING QUESTIONS WITH PNEUMOCOCCAL PNEUMONIA

As shown in Fig. (1), even today pneumonia continues to disproportionately affect the elderly, with *Streptococcus pneumoniae* (pneumococcus) believed to be the most common cause of community-acquired pneumonia in older adults [48]. Currently, a one-time vaccination against pneumococcal disease is recommended for those 65 years and older (Table 1). Vaccines against pneumococcus come in two forms, the pneumococcal conjugate vaccine (PCV), or the 23-valent non-conjugated pneumococcal polysaccharide vaccine (PPSV), both of which appear to have reasonable safety profiles [49]. The latter is CDC-recommended for use in the elderly, but despite this recommendation many studies have questioned the efficacy of the PPSV in the aged, with the general conclusion that while vaccination may help prevent invasive pneumococcal disease it is largely ineffective at controlling non-bacteremic pneumococcal pneumonia [16, 48]. In further support of this position, one recent meta-analysis of twenty-two PPSV clinical trials in adults concluded that pneumococcal vaccination was completely ineffective in preventing pneumonia, even in the targeted populations for which the vaccine is currently recommended [50]. However, as the authors of this study point out, a significant concern with the majority of the clinical trials was inaccurate diagnosis of outcomes, with most trials using a presumptive rather than definitive measure for pneumococcal pneumonia. This systematic error could undercut estimates of vaccine efficacy by incorrectly diagnosing pneumococcal pneumonia in those persons who are simply *S. pneumoniae* carriers. In contrast, a recent double blind, randomized, placebo controlled study in Japan has demonstrated promising results for PPSV in the elderly [51]. In this prospective study, nursing home residents (average age = 85 years) were randomly assigned to vaccine or placebo groups and followed for at least two years. While the outcomes against death from all-cause pneumonia and other causes were not statistically different between groups, focused analysis on pneumococcal disease demonstrated some dramatic results. The rate of diagnosed pneumococcal pneumonia was reduced by 62% in the vaccinated group ($p < 0.001$) and death from pneumococcal pneumonia dropped from 35.1% (13/37) to 0% (0/14).

While the debate regarding the true level of efficacy for the PPSV in elderly will likely continue, a separate but equally important question has emerged regarding vaccine format [48]. The conjugate vaccine, PCV, has proven successful in children, but can that success translate to the elderly? Several studies have investigated the immunogenicity of the PCV format in elderly adults. In one study of seniors, investigators tested various combinations of PPSV or PCV primary immunizations followed by PPSV or PCV boosts one year later [49]. In primary vaccinees PCV outperformed PPSV, with an approximate 2-fold advantage in specific antibody titers. However, this advantage was lost in vaccinees that had received a primary PPSV one-year previously suggesting prior exposure to PPSV could limit responses to the PCV format. A separate dose-ranging study, in persons aged 70-79 years who had received the PPSV at least five years previously, demonstrated that an increased dose of PCV (twice the childhood dose) could produce a booster effect [52] providing a possible workaround in cases of pre-existing immunity to the PPSV. However, in the absence of established correlates for protection against pneumococcal disease it is unclear if these modest gains in immunogenicity will translate into better protection for the elderly. Several ongoing clinical trials with PCV immunization in healthy adults [53, 54] and one randomized, placebo-controlled trial specifically focused on those ≥ 65 years of age [55] may help resolve what remains a difficult question and chart a better way forward for control of pneumococcal disease in this at-risk population.

SHINGLES PREVENTION IN THE ELDERLY; ARE SOME GROUPS LEFT OUT?

A major advance in vaccination for the elderly has been the recent introduction of a vaccine to reduce the incidence of herpes zoster [56]. Varicella zoster virus is the causative agent of chickenpox in the young, but infection with varicella results in a latent state that can lead to reactivation later in life and the appearance of herpes zoster, otherwise known as shingles. The lifetime risk for developing herpes zoster is estimated at 25-35% [57], but this risk dramatically increases in the elderly [58]. Although a live attenuated vaccine has been available for children for some time, it was unclear if adults already infected with varicella zoster could benefit from vaccination. The results of a large placebo-controlled clinical trial performed in the elderly (≥ 60 years) demonstrated that varicella vaccination could protect against shingles, with a reduction in herpes zoster incidence of up to 51% in vaccinees [59]. To achieve this result, the currently licensed Zostavax® uses approximately 14 times the dose found in the standard varicella vaccine for use in children. This increase in vaccine dose is needed to counteract the decrease in cell-mediated immunity (CMI) observed with advanced age [60]. Although immunosenescence may drive this decrease in CMI following vaccination, one should also consider that pre-existing immunity might play a role in limiting viral replication, thus attenuating the boosting effect. Nevertheless, while the overall efficacy was 51%, age stratification demonstrated significant differences among age groups, with those aged 60-69 years reaching 64% efficacy, subjects aged 70-79 years showing a 41% efficacy, and those ≥ 80 demonstrating only an 18% efficacy [61]. This trend

extended to severity of disease as a function of age. When examining herpes zoster-related complications, even in cases of breakthrough vaccinees did demonstrate an overall reduction in the incidence of postherpetic neuralgia (PHN) by 39%. However, in the oldest age group (≥ 80) this dropped to 26% relative efficacy, with 18.9% of herpes zoster cases in vaccinees demonstrating PHN compared to 25.5% in placebo controls. These results stress the difficulty in protecting the very elderly in our communities, even when using high-dose live attenuated vaccines.

CDC recommendations suggest that any person over the age of 60 receive one dose of Zostavax®, provided they have no medical conditions that constitute a contraindication [19]. From a safety standpoint, the vaccine was generally well tolerated in the elderly, with no significant differences in serious adverse events when compared to placebo. However, immunocompromised persons were specifically excluded from the pivotal efficacy study [59], and immunosuppression represents a formal contraindication to immunization [61]. These recommendations stem from the live nature of the vaccine, and concerns that immunocompromised persons might be at risk for severe adverse events following infection [62]. One report of the lower dose varicella vaccine in leukemic children did demonstrate an increased risk for rash, some of which contained live virus [63]. Studies of the higher dose herpes zoster vaccine have not been carried out in immunocompromised populations [62]. Given that the elderly often suffer from conditions considered contraindications, what options are available? Several studies have examined the use of a heat-killed vaccine in the elderly [62]. An initial report comparing heat-killed and live vaccines in healthy seropositive adults demonstrated similar antibody titers following vaccination [64]. In another study authors found comparable humoral and cellular immune responses in the elderly when immunizing with the standard varicella vaccine, or a heat-killed version of the same [65]. In terms of efficacy, a multi-dose schedule of heat-inactivated varicella vaccine demonstrated a lower incidence of herpes zoster (13%) versus a placebo control group (30%) during the year following immunization [66]. This study was performed specifically in an immunocompromised, at-risk group (autologous hematopoietic transplant patients) and demonstrated proof-of-principle for efficacy of an inactivated vaccine, even for the control of a latent viral infection. Such vaccines could be part of a broader strategy for preventing herpes zoster in the immunocompromised [62], filling an important gap that currently exists in the elderly population.

TRAVEL VACCINES FOR A SHIFTING DEMOGRAPHIC

With the growth of an older population interested in travel abroad, there is increasing attention to travel vaccines for the elderly [67]. As shown Table 1, many travel-related vaccines are currently available in the U.S. However, studies on their use and safety in the elderly are often quite limited. For instance, while Hepatitis A represents a significant health threat to travelers (up to 20 cases per 1,000 persons per month of travel) [68] relatively little is known regarding the immune response in the elderly [69]. As an inactivated vaccine, an adequate safety profile in the elderly would be expected. However, though antibody responses tend to be slower

and lower in older people, no study has examined responses in those >65 years of age [67], leaving a large gap in the medical knowledge concerning this important vaccine.

Similar to Hepatitis A, typhoid fever remains a significant health threat in many developing countries [67]. Currently, two vaccines are available for use, including a purified polysaccharide vaccine (parenteral use), as well as a live-attenuated vaccine for oral administration. Although typhoid vaccination is recommended for travel abroad to certain countries, almost nothing is known regarding immunogenicity in the elderly. The few studies that have examined typhoid vaccination in older age groups suggest reduced rates of seroconversion in relation to age, but these studies have involved subjects from endemic countries, and their relevance to non-endemic countries is uncertain [70]. For safety, again there is little known regarding geriatric use. However, when comparing vaccine types, it should be noted that live oral vaccination is contraindicated in all immunosuppressed persons [71], while the polysaccharide vaccine carries no comparable warning.

Japanese encephalitis is another common travelers vaccine, though the risk to travelers is relatively low, with estimates of <1 case per million travelers annually [72]. Worldwide, both inactivated and live attenuated vaccines are available, but only the inactivated vaccine is licensed for use in the U.S. Reactions to the vaccine are relatively mild, with common symptoms such as injection site tenderness, redness, and swelling, as well as more systemic effects including fever, headache, and malaise. As with other travel vaccines, studies in the elderly are limited. In a field trial conducted in a non-endemic region of Japan, responses in a group of 46 subjects ≥ 60 years of age were compared to 49 junior high school students following immunization [73]. While the authors concluded that responses in the elderly were not necessarily inferior to the young, only 35% of the elderly (compared to 20% of the students) demonstrated at least a 2-fold increase in serum antibody titers, suggesting a relatively poor response rate in both groups. Safety in the elderly has not been assessed, but based on experience with other inactivated vaccines, risk of severe adverse events would seem limited.

Vaccination against rabies is only recommended for travelers to specific remote regions, with risk primarily from infected dogs and monkeys. Rabies vaccines consist of inactivated virus, with several licensed products available in the U.S. All current U.S. vaccines are cell culture derived (removing concerns associated with older nerve tissue vaccines) and are generally well tolerated. Rabies represents one of the few travel vaccines with several studies performed in the elderly [74, 75]. In one study, researchers compared subjects 11-25 years of age to those over the age of 50 [75]. After 4 doses of vaccine, antibody responses in the younger cohort were 52% higher than the older vaccinees. These results were supported by a separate study, where researchers found a consistent decrease in antibody responses as a function of increasing age [74]. As with many other inactivated vaccines, the cell culture derived rabies vaccine is relatively safe, with no specific concerns associated with age [76].

In addition to the travel vaccines described above, several other vaccines are potentially available for use in the elderly, (measles-mumps-rubella, polio, cholera, etc.). Still, while many of these have been well studied in children, data concerning efficacy, immunogenicity and safety in elderly populations is not available [67]. In total, a substantial number of vaccines are available for use in the U.S. traveler (Table 1). Nevertheless, as demographics continue to shift towards an aged population, the medical community's lack of knowledge regarding the safety and performance of these vaccines in the elderly is becoming clear. Recent experience with a well-known travel vaccine illustrates the risks associated with such limited information in the elderly.

THE RISKS OF YELLOW FEVER VACCINATION IN THE ELDERLY

One of the most well-known travel vaccines for U.S. residents is the yellow fever vaccine. Yellow fever virus (YFV) is a member of the flavivirus genus, and is endemic in >40 countries [77], with up to 200,000 cases and 30,000 deaths reported annually [78]. In the U.S. approximately 250,000 U.S. civilians are vaccinated against YFV annually for travel to endemic countries [77], including older adults. The current U.S. vaccine, YFV-17D, is an attenuated live virus developed in the 1930s, and as with all viruses and vaccines, carries a risk of adverse events. Seroconversion rates, antibody titers, and studies regarding protective efficacy in the elderly are not available [67]. The majority of adverse events occur in infants (<9 months of age) and the elderly [79, 80], and may include mild symptoms such as redness, pain and swelling at the injection site, or systemic effects such as headaches, fever, and flu-like symptoms. However, recent reports regarding serious adverse events in older vaccinees have raised specific safety concerns in the elderly [81].

Though lethal adverse events are rare, they are primarily age-related. One serious side effect involving the nervous system (yellow fever vaccine-associated neurotropic disease [YF-AND]) can occur following vaccination, and is particularly hazardous for children under 9 months of age [79]. In the most dangerous cases the yellow fever vaccine can cause a severe multi-organ disease, termed yellow fever vaccine-associated viscerotropic disease (YF-AVD), a syndrome resembling wild-type yellow fever [79], with up to a 50% mortality rate. In the United Kingdom, YF-AVD has been reported at a rate of 1.3-2.5 cases per million vaccinations [82]. While young adults are at risk of lethal disease following YFV vaccination, a recent analysis of the Vaccine Adverse Event Reporting System data from 2000 to 2006 demonstrates that persons 60 years of age and older are at an increased risk for both YF-AND and YF-AVD [81]. During this period, the total incidence for YF-AND in the U.S. was estimated to be 8 cases per million civilian doses administered. For vaccine recipients 60-69 years of age, the incidence was up to 2-fold higher, at a rate of 16 cases per million doses. With advanced age (>70 years) the risk increased to an estimated 23 cases per million doses. The more severe viscerotropic syndrome, YF-AVD, demonstrated an even greater divergence with age. In the total population the incidence was 4 cases per million doses. However, those over 70 years of age showed a 6-fold increase in risk, with multiple associated fatalities. Strikingly, while the specific risk for

any particular trip must be evaluated on a case-to-case basis, the estimated overall risk for yellow fever in U.S. travelers to endemic regions has been put at 0.5-5 cases per million travelers [81]. This suggests that the combined risk in the elderly from severe adverse events (YF-AND and YF-AVD) following yellow fever vaccination could be up to 10 times the average risk associated with the disease itself in this travel demographic.

For yellow fever, the severe adverse events following vaccination are clearly tied to the live nature of the vaccine and associated with increasing age. Given the particular risk that the elderly face with YFV, do older travelers have any other choice? To date, no alternative vaccines for yellow fever are available. However, recent safety concerns have prompted some experts in the field to call for a change [83]. Indeed, early in the development of a yellow fever vaccine, some groups pursued inactivation as an alternative to live attenuated viruses [79]. Preliminary studies demonstrated promise in non-human primates [84], but results in humans were described as irregular [85]. One Brazilian group has reported the use of a pressure-inactivated YFV vaccine for protection in a mouse model of infection [86]. Recently, a U.S. group has published a non-clinical safety trial using a chemically inactivated whole-virus vaccine preparation [87]. While immunogenicity in small animal models was robust, in some instances immune responses in non-human primates waned rapidly. Nevertheless, with increased interest in this key travelers market, older adults may expect additional vaccine options, with appropriate safety and immunogenicity profiles, in the near future.

CONCLUSION

Based on projected increases in lifespan throughout the world, the elderly (>60 years of age) are expected to constitute nearly one-quarter of the entire global population by 2050 [1]. Considering reduced responses following vaccination, protecting the elderly from infectious disease will be an increasing challenge throughout the 21st century. Common vaccinations, such as influenza, can protect older populations, but at substantially lower rates than younger counterparts. This trend holds true with many vaccines, illustrating time and again a diminution in immune responses with increasing age. While many domestic and travel vaccines are available for use in the elderly, efficacy and safety are often unclear. Conventional strategies for boosting immune responses, such as the use of live attenuated vaccines, may offer only limited benefits in the elderly, and can raise serious safety concerns. Alternative strategies currently under development, including increased vaccine dosages, advanced adjuvants, and novel vaccine antigens, may provide safer and more efficacious vaccines for seniors in the future.

ABBREVIATIONS

LAIV	=	live attenuated influenza vaccine
PCV	=	pneumococcal conjugate vaccine
PPSV	=	non-conjugated pneumococcal polysaccharide vaccine
TIV	=	trivalent inactivated influenza vaccine

YFV	=	yellow fever virus
YF-AND	=	yellow fever vaccine-associated neurotropic disease
YF-AVD	=	yellow fever vaccine-associated viscerotropic disease.

CONFLICT OF INTEREST STATEMENT

Dr. Amanna has a financial interest in Najft Technologies, Inc., a company that may have a commercial interest in the results of this research and technology.

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