

WHAT'S HOT

A Newsletter of



IN THIS ISSUE:

Addressing the Complex Impact of Immunosenescence: The Value of Vaccination

Introduction 1

Immunosenescence and Factors That Affect It 2

Contribution of Immunosenescence to Vaccine-Preventable Diseases 3

Vaccine-Preventable Diseases and Thrombotic Events 5

Strategies to Overcome the Effects of Immunosenescence 7

Summary 8

Introduction

Immunosenescence refers to the changes in the immune system with aging and relates to the progressive decline of innate and adaptive immune responses.¹ Clinical outcomes of immunosenescence include an increased risk for occurrence and severity of infections and autoimmune disorders. The most common infections of older adults include urinary tract infections, skin infections, and pneumonia; vaccine-preventable infections, such as influenza, pneumococcal infections, and reemergence of latent varicella zoster infection in the form of herpes zoster, or shingles, all increase with aging. Older adults with vaccine-preventable infections such as influenza and pneumonia often present atypically and may have a prolonged course.^{2,3}

Among vaccine-preventable infections, pneumonia and influenza are the most common causes of infection-related hospitalization and death in people aged 65 years and older; and influenza, pneumococcal disease, and herpes zoster rank as the top three vaccine-preventable infections in terms of economic burden, costing over \$8 billion annually in the United States.⁴ The risk for shingles increases substantially with age, along with the risk for developing the functionally

disabling postherpetic neuralgia. This change in risk is due to the decline in immunologic function with age. Immunosenescence also results in the reduced efficacy of vaccines in older adults—the population that needs protection the most.

Immunosenescence translates into “inflammaging” (aging-related, low-grade, chronic inflammation) and plays into indirect outcomes of inflammation, including thromboembolic disease such as cardiovascular and cerebrovascular events. This issue of the *What's Hot* newsletter will review some of the causes, consequences, and efforts to mitigate the effects of immunosenescence on vaccine response; it will address pertinent issues on vaccine-preventable infections and other outcomes as well as reasons to continue working toward the Healthy People 2020 vaccination goals (Table 1).^{5,6} ♦

Immunosenescence results in the reduced efficacy of vaccines in older adults—the population that needs protection the most.

Faculty

Yasin Abul, MD

Geriatrician
Rhode Island Hospital
Warren Alpert Medical
School of Brown University
Providence, Rhode Island

David H. Canaday, MD

Associate Professor
Case Western
Reserve University
Associate Director
Geriatric Research
Education and
Clinical Center
Louis Stokes VA Hospital
Cleveland, Ohio

Arvydas Ambrozaitis, MD

Professor
Institute of
Clinical Medicine
Infectious, Chest,
Dermatovenereology, and
Allergology Clinic
Vilnius University
Vilnius, Lithuania

Edward H. Davidson, PharmD, MPH

Partner, Insight
Therapeutics, LLC
Assistant Professor
Glennan Center
for Geriatrics
and Gerontology
Eastern Virginia
Medical School
Norfolk, Virginia

Stefan Gravenstein, MD, MPH

Professor
Warren Alpert Medical
School of Brown University
Investigator
Center of Innovation
Providence VA Hospital
Clinical Director
Healthcentric Advisors
Providence, Rhode Island

Table 1. Healthy People 2020 Baseline Data and Goals

OBJECTIVES	BASELINE DATA 2008	HEALTHY PEOPLE 2020 GOALS
INFLUENZA VACCINE		
Adults 18 to 64 years old	25%	80%
High-risk adults 18-64 years old	39%	90%
High-risk adults 65 years and older	67%	90%
Institutionalized adults 18 years and older*	62%	90%
Health care personnel	45%	90%
PNEUMOCOCCAL VACCINE		
Adults 65 years and older	60%	90%
High-risk adults 18 to 64 years old	17%	60%
Institutionalized adults*	66%	90%
HERPES ZOSTER VACCINE		
Adults 60 years and older	7%	30%

* Baseline data, 2006.

Source: References 5 and 6.

Immunosenescence and Factors That Affect It

The normal aging process is determined by genetic disposition and influenced by external factors that affect severity of immunosenescence. These include nonmodifiable sex differences, comorbidities, oxidative stress, chronic viral infections (e.g., cytomegalovirus or possibly Epstein-Barr virus), and potentially modifiable risks related to sociodemographic factors, unhealthy habits, medications, malnutrition, chronic stress, and exercise.^{3,7,8} Iatrogenic immunosuppression by biologic agents, which have seen increased use among older adults, is a contemporary concern regarding vaccine response.⁹ Oxidative stress is thought to be a major factor of accelerated aging given the possible influence of an increased pace of telomere shortening secondary to DNA damage.¹⁰

There are multiple specific defects in the aging immune system that

culminate in immunosenescence and likely are additive in their effects. The defects described in older individuals encompass all of the cells that are critical for optimal vaccine-induced responses and many diseases that increase in incidence with age. Vaccine response-relevant defects include defects in antigen presenting cells, T cells, and B cells. Dendritic cells and macrophages are involved in the initial vaccine uptake and presentation. There is evidence of a reduced phagocytic capacity and cell migration in these cells in older individuals.^{11,12} Most vaccines are T-dependent meaning that they require T cell help to elicit optimal titers of high-affinity antibodies. T follicular helper cells are required for this and have been found to be reduced in number and in their helper function with aging.^{13,14} B cells, the cells that produce the antibodies that are one of the most critical

effector molecules in protection induced by vaccine, have multiple defects. The percentage of naive B cells in the periphery and lymph nodes is reduced with age while the number of memory B cells increases.¹⁵ A defect in isotype switching and somatic mutation leading to a decline in high-affinity immunoglobulin G antibodies also has been described.¹⁶ In addition, there is reduced B cell diversity, fewer antigen-specific antibodies, and higher numbers of antigen-nonspecific antibodies produced in older individuals.^{17,18}

Immunosenescence can be described as an outcome of immune dysregulation. Collectively, these changes result in more than just poor vaccine responses in late life; they also allow infections to run unchecked longer and symptoms from the underlying disease driven by cytokines, including the cytokine storm, to alter the clinical

presentation, where potentially even lethal infection appears clinically more benign. The clinical relevance of this change means that older adults who are infected present differently and their infection may go unrecognized. For example, older adult patients admitted to the hospital for other diagnoses often go undiagnosed for their influenza, and the contribution of influenza as the cause of the hospitalization event gets missed.

In a recent clinical trial involving over 50,000 long-stay nursing home residents over 65 years of age, we described a difference in hospitalization rates where, at the facility-wide level, residents were offered either standard-dose or high-dose influenza vaccine. There were nearly 300 fewer

hospitalizations of residents in the facilities that offered the more efficacious high-dose vaccine than those that offered a less immunogenic vaccine. Yet, the number of individuals who had a Medicare claim of influenza was only 27 (6 from facilities receiving the more immunogenic high-dose vaccine), and two-thirds of that hospitalization difference of nearly 300 could be accounted for by hospitalizations for nonrespiratory primary diagnoses involving the cardiovascular system. The clinicians had either not listed the influenza diagnosis as part of their insurance claim or influenza presented in an unrecognizable form; in these patients, we suggest that immunosenescent consequences of altered presentation and

Older adult patients admitted to the hospital for other diagnoses often go undiagnosed for their influenza, and the contribution of influenza as the cause of the hospitalization event gets missed.

immune dysregulation and a prothrombotic state resulted in a cardiovascular rather than respiratory presentation for hospitalization.^{19,20} We further explore the relationship between these vaccine-preventable infections and thrombotic events later in this newsletter. ♦

Contribution of Immunosenescence to Vaccine-Preventable Diseases

Vaccines in general, whether against influenza, *Streptococcus pneumoniae*, or herpes zoster virus, are intended and licensed to protect against specific pathogens. Because these vaccines have been less effective in the older adult population,²¹⁻²⁴ there has been an ongoing effort to design better vaccines—and this has met with some success. This brief overview describes the effectiveness of the currently available vaccines to prevent influenza, pneumococcal disease, and shingles.

Influenza Vaccine

More than 90% of influenza-related mortality reported annually occurs in patients older than 65 years of age and older adults also experience considerably increased morbidity from the disease.²⁵ Older adults are prone to infections owing to their

associated comorbidities, frailty, and nutritional deficiencies; the combination of all these predisposing and aggravating factors can cause additional morbidity in the form of changes in activities of daily living, strokes, and heart attacks.^{26,27} Influenza vaccine effectiveness has been thwarted by age-related declines in vaccine response.²⁸

In recognition of age-related declines in vaccine response, newer vaccines have been introduced into the market with improved immunogenicity and the goal of improving overall effectiveness. These include two higher dose vaccines—Fluzone High-Dose (Sanofi Pasteur) with four times the antigen; and Flublok (Protein Sciences), a recombinant vaccine with three times the antigen—and an adjuvanted vaccine, Fludax (Seqirus), with

MF59 adjuvant. The evidence for improved effectiveness in older adults is strongest for the highest dose vaccine, with two major randomized controlled trials^{19,29} over different influenza seasons indicating an approximately 24% relatively greater reduction in laboratory confirmed influenza in community-dwelling older adults²⁹ and a 12.7% reduction in respiratory hospitalization of nursing home residents compared with standard-dose influenza vaccines. Two other metadata-type studies report concordant findings.^{30,31} The adjuvanted influenza vaccine has several nonrandomized controlled studies suggesting a similar effect size.³²⁻³⁴ A single randomized controlled trial indicated that the recombinant quadrivalent vaccine compared with standard-dose quadrivalent vaccine resulted in a 30% reduction in influenza-like illness.³⁵

Pneumococcal Vaccine

Pneumococcal disease can cause significant morbidity and mortality in older adults. The incidence of pneumococcal disease and the mortality rate tend to increase after age 50 years and these increases are more often seen after age 65 years.³⁶ As a result of these risks, an effective vaccine can fill a significant need for older populations. The current vaccine regimen for individuals older than 65 years of age involves two vaccines. One is the 23-valent pneumococcal polysaccharide vaccine (PPSV23; Pneumovax—Merck) and the other is the 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar 13—Pfizer). PPSV23 is less immunogenic but covers 10 more strains than PCV13, while PCV13 is more immunogenic with better immunologic memory. A large double-blind randomized controlled trial in adults aged 65 years and older showed 45% efficacy of PCV13 in preventing strain-matched community-acquired pneumococcal pneumonia.³⁷ The Cochrane meta-analysis of PPSV23 concludes that it prevents invasive pneumococcal disease in adults.³⁸ Maruyama and colleagues performed a double-blind placebo-control randomized trial in nursing home residents and found PPSV23 prevented pneumococcal pneumonia and

reduced mortality, indicating effectiveness in a particularly frail population.³⁹ Because each vaccine, PCV13 and PPSV23, offers potentially additive advantages,⁴⁰ the recommended schedule from the Centers for Disease Control and Prevention includes the use of both vaccines.⁴¹

Shingles Vaccine

There are now two vaccines for shingles prevention approved by the U.S. Food and Drug Administration (FDA). Zostavax (Merck) is a live attenuated zoster vaccine that was FDA approved in 2005. Including all groups of individuals aged 60 years and older that were studied, Zostavax had an efficacy of 51% in protecting against herpes zoster and reduced postherpetic neuralgia by 66.5%.²⁴ Most of the reduction in postherpetic neuralgia is a consequence of not getting shingles in the first place. In other words, for the subset that developed shingles despite vaccination, the risk for developing postherpetic neuralgia was not reduced as much. Examining the efficacy by decades of life, the vaccine is 70% effective in 50- to 59-year-old adults, 64% in 60- to 69-year-old adults, 41% in 70- to 79-year-old adults, and only 18% in those older than

80 years of age.⁴² Because of both the declining efficacy with age and room for improvement in all age groups, there has been much work to evaluate and bring to market a more immunogenic vaccine.

In October 2017, the FDA approved a new adjuvanted herpes zoster subunit vaccine (Shingrix—GlaxoSmithKline). In addition to requiring two doses for full effectiveness, Shingrix differs from the live vaccine in several important ways. It is a subunit glycoprotein vaccine that is stored at normal refrigeration temperatures rather than requiring freezer storage, and it is adjuvanted with AS01. Two large studies were conducted; one focused on adults aged 50 years and older and the other on those aged 70 years and older.^{43,44} The efficacy reported for these studies remained high even in the group of adults older than 80 years of age, at 89%, and led to the majority vote for a preferential recommendation over the live vaccine by the Advisory Committee on Immunization Practices (ACIP) in October 2017. The final published recommendations were not available at the time this newsletter went to press, but the ACIP discussion suggested that individuals vaccinated more than 5 years earlier with the live vaccine could also be vaccinated with the adjuvanted subunit vaccine. There were so few cases of zoster in the vaccine group that the ACIP was not able to assess whether the vaccine confers an increased benefit to prevent postherpetic neuralgia beyond that of the primary prevention of shingles. Because of the new preferential vaccination, including revaccination with the new subunit vaccine for individuals previously vaccinated with the live vaccine, progress toward the Healthy People 2020 zoster vaccine goal may be affected. ♦



Vaccine-Preventable Diseases and Thrombotic Events

The significant noninfectious consequences of these infectious diseases as a major cause of morbidity and mortality are beginning to emerge and may represent a significant additional target of vaccinating against influenza, pneumococcus, and shingles. The association between influenza and increased mortality from cardiovascular events was first recognized in the early 1900s after an influenza outbreak and pandemic in both Europe and the United States.⁴⁵ The more general link to infection, specifically lower respiratory tract infections and urinary tract infections,⁴⁶ and reemergent latent infection such as shingles⁴⁷ and the increased risk of vascular events including myocardial infarction, stroke, and venous thromboembolism has come later.⁴⁸⁻⁵²

Currently, estimates from pooled data indicate that influenza, influenza-like illness, or respiratory tract infection increases the risk of myocardial infarction (odds ratio, 2.01; 95% confidence interval [CI], 1.47–2.76), and this risk is highest among those older adults with known cardiovascular diseases.⁵³⁻⁵⁵ Similarly, it has been previously shown that the 1918 pandemic influenza virus and *S. pneumoniae* coinfection caused activation of coagulation and led to widespread pulmonary thrombosis.⁵⁶

Both in vitro and in vivo studies showed the link between community-acquired pneumonia and cardiovascular adverse events and complications.⁵⁷ Cangemi and colleagues found that 18% of individuals hospitalized with community-acquired pneumonia had a cardiovascular event (i.e., myocardial infarction, new episode atrial fibrillation, or both events); the proportion with cardiac complications increased with age and the severity of pneumonia as determined by the pneumonia severity index.⁵⁸

Herpes zoster has also been associated with thromboembolic events.^{47,59,60} The risk of myocardial infarction or stroke has been known to be increased after an episode of shingles.^{60,61} There is an association between the acute expression of herpes zoster and either or both cerebrovascular and cardiovascular disease. The stroke and myocardial infarction risk increases transiently for a few months after the development of herpes zoster.⁵² It was also reported in the meta-analysis of 12 studies by Erskine and colleagues that there is an increase in cerebrovascular and cardiovascular events associated with herpes zoster and herpes zoster ophthalmicus with a specific increased risk for stroke near 33% [95% CI, 1.22–1.46] for the first 3 months after herpes zoster and 22% [95% CI, 1.15–1.29] up to a year.⁶¹ Although exact mechanism is obscure, herpes zoster could also induce systemic inflammation, autoimmune responses, or hemodynamic changes that result in a cardiovascular event.^{50,52,62} Individuals who develop herpes zoster have elevated C-reactive protein (CRP), among other inflammatory markers, ahead of the herpes zoster event that are similar to markers that identify cardiac risk.

Mechanisms for Increased Cardiovascular Events Following Infection

There have been several theories of what drives the thrombotic risk of vaccine-preventable infections, and several of these directly relate to immunosenescence, such as the rising levels of interleukin-6 (IL-6) and CRP with age and other inflammatory markers. The mechanism how influenza increases the risk of cardiac events is not well defined, but it has been proposed that it might be secondary to destabilization and rupture of susceptible

atherosclerotic plaques.⁶³ For viral infections, direct viral infection of vascular cells can increase procoagulant factors including thrombin and von Willebrand factor, affect thromboxane levels, and may also decrease expression of thrombomodulin,⁶⁴ any of which could influence the risk of a thrombotic or thromboembolic event. In addition to direct vascular invasion, increased inflammatory response locally and systemically might induce local and systemic thrombotic events that are probably more important than direct vascular invasion, perhaps particularly relevant to influenza infection. Local and systemic cytokine response during experimental human influenza A virus was shown previously by Hayden and colleagues⁶⁵ with elevated IL-6 and interferon-alpha in nasal lavage fluids, and increased IL-6 levels in circulation. IL-6, which is a proinflammatory cytokine with antiviral effects, has an important role through its prohemostatic effects and could cause pathologic thrombosis and vascular plaque instability, and it was shown that cytomegalovirus and influenza have potential to modulate the in vitro production of IL-6 by human endothelial cells.⁶⁶

In addition to inflammatory activity and a dominant prothrombotic state, increased biomechanical stress on coronary arteries, variations in the coronary arterial tone, altered hemodynamic homeostasis, and myocardial metabolic balance have been suggested to contribute to the increased risk of cardiovascular outcomes with infection.⁶⁷⁻⁶⁹

Gerontologists argue that a feature of aging is increased inflammation and have coined the term “inflammaging.” The pro-inflammatory state is essentially

Influenza increases the risk of myocardial infarction, and this risk is highest among older adults with known cardiovascular diseases.

a consequence of immune dysregulation, or more simply, immunosenescence.⁷⁰ It is a significant contributing reason why thromboembolic disease increases with age along with the consequences of these outcomes when vaccines fail.

Vaccines for the Prevention of Cardiovascular Outcomes

Given that a quarter or more of people hospitalized with pneumonia develop a major acute cardiac complication during their hospital stay that is associated with a 60% increase in short-term mortality,^{67,69} it makes sense that both influenza and pneumococcal pneumonia could provoke a cardiovascular outcome. If this assumption is correct, then vaccines to prevent influenza and pneumococcal pneumonia should also be able to prevent consequent cardiovascular events, regardless of reducing the inflammation associated with pneumonia.

The meta-analysis by Udell and colleagues of five clinical trials totaling more than 6,000 patients with varying degrees of cardiovascular risk evaluated the link between influenza vaccine and cardiovascular outcomes.⁷¹ Influenza vaccine was associated with 36% lower incidence of major cardiovascular events within a year of vaccination. They calculated 1.7 major cardiovascular events were prevented for every 100 persons with cardiovascular disease and vaccinated against influenza. In

patients with recent acute coronary syndrome, influenza vaccination was associated with a 55% lower risk of major adverse cardiovascular events (MACE).

In an unblinded prospective randomized controlled trial with a blinded endpoint, Phrommintikul and colleagues⁷² evaluated the impact of influenza vaccination on MACE. MACE outcomes included death, hospitalization from acute coronary syndrome, heart failure, and/or stroke. MACE occurred less frequently in the vaccinated group than in the control group (9.5% vs. 19.3%; adjusted hazard ratio [HR], 0.67 [0.51-0.86], $P = 0.005$; unadjusted HR, 0.70 [0.57-0.86], $P = 0.004$). There was no mortality or cardiovascular mortality difference. The beneficial effects associated with influenza vaccine persisted after adjustment for variables affecting MACE and in every subgroup of patients.

In a Cochrane analysis, Clar and colleagues included eight influenza vaccination trials that compared a population that received either placebo or no vaccination with 12,029 participants who received at least one vaccination to evaluate vaccine-related reduction in cardiovascular mortality and combined cardiovascular events.^{55,73} They concluded that influenza vaccination was associated with a reduction in cardiovascular disease and MACE; however, they cited a risk of bias in some studies, making for inconsistent results and a need for additional higher-quality evidence to confirm the relationship.

Presently, a clinical trial of high-dose versus standard-dose influenza vaccine in adults with known recent myocardial infarction or heart failure is being conducted to assess whether the high-dose vaccine has a differential benefit, even including those younger than 65 years of age (NCT02787044).

This trial is currently recruiting participants. It is hoped that outcomes of the trial will settle remaining uncertainty about the likely benefits of influenza vaccine in the reduction of cardiovascular outcomes for this population.

The first study of the potential preventive effect of influenza vaccination on venous thromboembolism was done by Zhu and colleagues. They found that influenza vaccination reduced the risk of venous thromboembolism with an average reduction of 26% in the risk of venous thromboembolism in the overall study population.⁷⁴

The meta-analysis conducted by Vlachopoulos and colleagues showed that pneumococcal vaccination is related to the decrease in risk of cardiovascular events and mortality. This review also showed a protective effect of pneumococcal vaccination that tends to increase at older age and in populations with high cardiovascular risk factors.⁷⁵

A study by Minassian and colleagues on acute cardiovascular events after herpes zoster was a self-controlled case series analysis in vaccinated and unvaccinated older residents of the United States. The authors reported that stroke and myocardial infarction rates were transiently increased after exposure to herpes zoster and there was no evidence for a role of live attenuated zoster vaccination in these associations.⁵² The power of the study was limited from the point of vaccination effect because the number of vaccinated individuals was limited. There are no data in this area yet regarding the recently FDA-approved adjuvanted zoster vaccine. Data will likely emerge in the coming years to better assess any thromboprotective benefit from the more highly efficacious adjuvanted zoster vaccine. ♦

Strategies to Overcome the Effects of Immunosenescence

Vaccine makers have made a number of efforts to develop vaccines specifically targeted at overcoming immunosenescence in older persons by employing either of two primary strategies: increasing the dose of the immunogen or using an adjuvant.

The strategy to increase the dose of the immunogen has been employed in three currently licensed products. One is the high-dose influenza vaccine that is identical in composition to the standard-dose influenza vaccine except this high-dose vaccine has 4-fold higher antigen doses. This high-dose influenza vaccine has been shown to have increased immunogenicity with higher antibody titers elicited and a 24% increased clinical efficacy compared with the standard-dose vaccine.⁷⁶⁻⁷⁸ The second product is the recombinant influenza vaccine, which has 3-fold more antigen than the standard influenza vaccine; it has similar immunogenicity by traditional measures to standard-dose vaccine⁷⁹ but evidences improved clinical protection in older individuals.³⁵ The third product is the live attenuated zoster vaccine. It has a 14-fold higher dose than the chickenpox vaccine, although it is the same live attenuated strain. These vaccines have this similar higher dose method to enhance their efficacy, however their immunologic goals are substantially different as the zoster vaccine elicits cell-mediated immunity for protection whereas the primary goal of the influenza vaccine is to enhance anti-influenza humoral immunity.

Another strategy to overcome poor antibody response to vaccines employs the use of an adjuvant. Adjuvants, which increase the immune response to the vaccine antigen, are widely used in many vaccines but not until recently (in the United States) for influenza or shingles. An adjuvanted

influenza vaccine has been available in Europe since the 1990s. It was approved in the United States in the last 2 years. Use of the adjuvant allows vaccine manufacturers to use even less antigen than the standard-dose vaccine and immunogenicity studies have shown better heterologous immunity to drifted influenza strains.^{80,81} The adjuvanted influenza vaccine has the potential advantage to provide more protection in an influenza season when the predominant clinical strain does not exactly match the strain in the vaccine. In October 2017, a new vaccine was licensed with the AS01 adjuvant to prevent shingles. This vaccine, in contrast to the higher dose live shingles vaccine, generates substantially greater immunity in older individuals. There was also a phase 3 trial of a respiratory syncytial virus vaccine in older adults that had disappointing results (NCT02608502); this trial used the unadjuvanted form of vaccine and it did not appear to have efficacy. The investigators are testing their vaccine construct in older populations with an adjuvanted form of the vaccine.

Several indirect strategies can be employed to help overcome the hazards of infection risks derived from immunosenescence. Such strategies do not involve the older person's

immune system. Some are within the control of the individual and some are group or even societal measures. For example, an individual could avoid getting infected during the height of the influenza season by avoiding social situations, including social distancing. Group or societal interventions can have even larger benefits. As influenza spreads from person to person, older adults often contract the disease after contact with children or other younger adults, including potential health care providers. These contacts are typically younger and in groups for whom influenza vaccine is most effective. There are several reports associating influenza vaccination uptake in health care workers with a reduced risk of influenza outbreaks in the long-term care settings where they work.⁸²⁻⁸⁴ Even in the community setting, data show that influenza-related illness in older populations is reduced inversely proportional to influenza vaccine uptake in younger adults thus supporting the concept of herd immunity.⁸⁵

What We Need in the Future

We need to continue research to develop vaccine formulations targeting the immunosenescent and multimorbid population of older adults, and the research needs to



address the features that make older adults more susceptible to these vaccine-preventable diseases. Older populations are often understudied and systematically excluded from clinical trials due to the complexity of their inclusion; this approach is short-sighted given that seniors are the adult population with the greatest need. The older immune system, while it has many specific

defects as previously discussed, still has sufficient functional reserve available for boosting as evidenced by the success of increased dose and adjuvant strategies.

Furthermore, we need knowledge specific to the care of older adults regarding if and when to boost the *S. pneumoniae* and shingles vaccines. The combination of a more durable vaccine response and a

universal influenza vaccine would have exceptional added value for our vaccine armamentarium. There also remains a debate regarding whether to administer certain vaccines at younger ages as an approach to generate more durable responses. These are essential questions. There is still much research to do in the field of vaccines to safeguard the health of older adults. ♦

Summary

Immunosenescence has proved challenging in vaccine design and has been a key feature relating to increasing infectious disease morbidity and mortality as well as vaccine failure in older adults. One lesser appreciated aspect of immunosenescence is its relationship to “inflammaging” and the increasingly prothrombotic state that comes with advancing age and thromboembolic risk that increases during the time following infection. With influenza vaccine, we have

seen a new promise of improved outcomes that are beyond the targeted infection and have the potential to affect a major class of morbidity and mortality—vascular events such as heart attacks and strokes. Future research needs to include other vaccines for infections and treatments for common inflammatory diseases that have the potential for far reaching benefits affecting functional outcomes toward morbidity compression, thereby adding life to years.

Vaccine improvements have come a long way in the last two decades. Research has added several substantially improved vaccines and vaccine design approaches, including increased dose offerings, adjuvants, and conjugation, all contributing to greater protection from clinical disease for older adults. As we continue the drive to make “better vaccines,” the challenge to increase vaccine uptake remains a crucial aspect of reducing the incidence of vaccine-preventable diseases—no vaccine is effective when left on the shelf. ♦



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