Workshop on Immunizations in Older Adults: Identifying Future Research Agendas

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Goals for immunization in older adults may differ from those in young adults and children, in whom complete prevention of disease is the objective. Often, reduced hospitalization and death but also averting exacerbation of underlying chronic illness, functional decline, and frailty are important goals in the older age group. Because of the effect of age on dendritic cell function, T cell-mediated immune suppression, reduced proliferative capacity of T cells, and other immune responses, the efficacy of vaccines often wanes with advanced age. This article summarizes the discussion and proceedings of a workshop organized by the Association of Specialty Professors, the Infectious Diseases Society of America, the American Geriatrics Society, the National Institute on Aging, and the National Institute of Allergy and Infectious Diseases. Leading researchers and clinicians in the fields of immunology, epidemiology, infectious diseases, geriatrics, and gerontology reviewed the current status of vaccines in older adults, identified knowledge gaps, and suggest priority areas for future research. The goal of the workshop was to identify what is known about immunizations (efficacy, effect, and current schedule) in older adults and to recommend priorities for future research. Investigation in the areas identified has the potential to enhance understanding of the immune process in aging individuals, inform vaccine development, and lead to more-effective strategies to reduce the risk of vaccine-preventable illness in older adults. **J Am Geriatr Soc 58:765–776, 2010.**

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Median life expectancy in the United States rose steadily through the 20th century, from the age of approximately 50 in 1900 to the current age of almost 80. Much of the increase in longevity can be attributed to reduced infection-related deaths in children and young adults achieved through sanitation, immunization, and antibiotics. An aging population has resulted in people aged 65 and older constituting the most rapidly growing segment of the U.S. population. This is a global phenomenon, with median life-expectancy predicted to rise into the 70s in most countries by 2050.[1] Older adults are more vulnerable to most infectious diseases, including those considered "vaccine preventable"[2] (e.g., influenza),[3] placing a large burden on healthcare resources.[4] To assess the current evidence base and identify and prioritize research in the area of vaccine-preventable illness in older adults, a workshop sponsored by the John A. Hartford Foundation was held in Washington, D.C., in December 2008, bringing together members of the immunology, infectious diseases, geriatric medicine, and gerontology communities. The proceedings of this workshop are summarized in this manuscript. The meeting focused on the basic and translational science of vaccine biology but did not address the real and important matters of access, vaccine uptake, or population-based strategies

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(e.g., immunization of healthcare workers and close contacts) that influence the rate of vaccine-preventable illness in older adults.[5]

GOALS OF IMMUNIZATION IN OLDER ADULTS

Although the goal of immunization for most childhood illnesses (e.g., measles, polio) is elimination of clinical disease, this is often unrealistic for older adult populations with diminished immunity and impaired vaccine responses. The goals of immunization in older adults are to prevent serious illness, hospitalization, and death, but benefits relating to exacerbation of underlying chronic illness, functional decline, and frailty are other worthy endpoints, although they are rarely examined in clinical trials. These endpoints are more difficult to measure and harder to specifically attribute to the organism(s) targeted by vaccines, often leading to conflicting evidence of vaccine efficacy in older adults. For example, although some investigators have found that administering the influenza vaccine to community-dwelling individuals aged 65 and older leads to significant reductions in risk of hospitalization for pneumonia or influenza, and death,[6] others have documented little or no effect, particularly in those aged 70 and older with significant comorbidities.[7,8]

Exacerbation of underlying illness is a major contributor to infection-related morbidity and mortality in older adults, but the mechanisms that lead to adverse outcomes have not been fully elucidated. Some data suggest that inflammation after an infectious illness is prolonged in older adults, with significant elevations of serum amyloid A and C-reactive protein that may contribute to triggering events such as myocardial infarction and stroke.[9] A few studies suggest that vaccines can significantly reduce this risk.[10,11]

A major objective of preventive interventions in older adults is the reduction of catastrophic disability, defined as loss of independence in three or more activities of daily living (ADLs).[12] Nearly three-quarters of those experiencing catastrophic disability have been hospitalized with stroke, congestive heart failure, pneumonia, ischemic heart disease, cancer, or hip fracture.[12] Influenza and other viral infections have been linked to catastrophic disability in several studies.[13,14] The degree of underlying comorbidity, measures of functional reserve (e.g., walking speed), and evidence of changes in adaptive immunity common, but not universal, in advanced age predict risk of adverse outcomes after vaccine-preventable illnesses. To better understand vaccine responses in adults with frailty or advanced age, clinical trials are needed that measure relevant risks and outcomes in these populations. The benefit of vaccination might not be consistently measurable in some studies, because the benefit of preventing catastrophic or other disability increases in older adults (e.g., because of the inability to see decline in function because of low starting point on available validated scales, i.e., a "floor" effect). It is important that a means of measuring vaccine efficacy in frail adults be addressed in the study of new vaccines.

EFFECTS OF AGING ON IMMUNE FUNCTION

Older individuals experience lower quantity and quality of the immune response after immunization than young adults[15] as a result of disease- and age-related changes in multiple aspects of the immune system. A complete review of immune senescence is beyond the scope of this article, but major aspects pertinent to vaccine responses are summarized below, and the reader is referred to recent publications for a more-complete review.[16–18]

Antigen-Presenting Cell Function

Antigen-presenting cells (APCs) are specialized cells that present foreign substances and send out signals to T cells, initiating an immune response. Although B cells, macrophages, and other cells can act as APCs, the major APC for most vaccines is the dendritic cell (DC). DCs present antigen and provide co-stimulation signals and cytokine that drive T cell and B cell responses. The capacity for older DCs to present antigen is well preserved, but aging ($\geq$65) appears to alter cytokine production significantly[19] and can affect co-stimulation; pattern recognition receptors such as Toll-like receptors (TLRs) typically trigger both. TLRs recognize microbial products (e.g., lipids, proteins, ribonucleic acid, deoxyribonucleic acid); specifically, TLR9 recognizes nucleic acid sequences and multiple cytosines and guanines that are more common in viruses than mammalian cells. Plasmacytoid DCs demonstrate poor upregulation of interferon regulatory factor (IRF) 7 after TLR9 activation, and greater oxidative stress contributes to this defect, but other studies demonstrate that the age-associated defect in interferon-alpha (IFNα) production is reversible. After augmenting the production of IFNα in older hosts, immune function (as measured according to viral clearance) is similar to that of young adult mice.[20]

Human studies of DCs are limited. In human peripheral blood monocytes (from which DCs are derived) less surface expression of TLR1/2 and agonist-induced tumor necrosis factor-α and interleukin-6 production but unchanged expression of TLR4 was demonstrated.[19] TLR-induced defects in cytokine production and expression of the co-stimulatory molecule CD80 in human DCs appear more extensive than previously observed in monocytes and are highly associated with influenza vaccine antibody response.[19] Expression of PRAT4A, a protein associated with TLR4 that is required for multiple TLR responses, is also lower in older adults.[21]

T Cells and Adaptive Immunity

Studies of T cell immune senescence are most extensive in mouse models that demonstrate some age-related changes intrinsic to the T cell, but other mouse models are dependent on the T cell residing in the older host.[22] The production of new naive T cells and their number and function in the periphery declines with age, gradually, through adolescence and early adulthood; the involution of the thymus appears to be the major contributor to this change. Older T cells respond less well to antigenic stimulation (reduced proliferation and cytokine production) than young T cells. Furthermore, poor B cell proliferation, germinal center formation, and immunoglobin (Ig)G production to T-dependent antigens evidence the ability of older T cells to assist B cell responses to vaccines.[23] Mouse studies also demonstrate that the environment functionally inhibits young T cells transferred into older hosts, perhaps because of

demonstrated age-related increases in T-regulatory or other cells that inhibit immune responses.[24]

Primate studies also suggest that intrinsic and extrinsic factors contribute to poorer T cell function with age. The naïve T cell pool, those T cells not yet exposed to antigen recognized by their specific T cell receptor, exhibits greater cycling in older nonhuman primates in direct proportion to the extent of depletion of naive T cells. This is consistent with the "antagonistic pleiotropy" theory of aging—that the same mechanisms that provide advantages early in life (e.g., maintenance of the naive T cell pool by low-level cycling, perhaps in response to IL-7) tend to enhance the loss of naive T cells by homeostatic proliferation and memory conversion late in life.[25] Investigators have documented several distinct types of age-related disturbances in T cells that affect T cell homeostasis. Repertoire balance, the breadth of antigens to which the T cell pool can respond, is poorer with age, impairing the ability to respond to a previously unencountered pathogen[26] (Figure 1). In the CD8+ T cell compartment, there is a similar loss of diversity and accumulation of a narrow repertoire of oligoclonal memory T cells directed at viral pathogens that persist throughout life (e.g., cytomegalovirus (CMV)). An expanded group of senescent CD8+ T cells directly correlates with poorer responses to vaccines,[27,28] perhaps because of the inhibitory cytokines produced by these senescent CD8+ T cells. (See Mechanisms Underlying Immune Senescence below.)

Human studies reveal age-related changes in T cell function similar to those observed in rodent and nonhuman primate models. These include contraction in T cell receptor diversity and imbalance of functional T cell subsets, as described above. Impaired T cell activation and signaling, poor T cell proliferation, and aberrant gene expression is also noted.[29] The earliest epidemiological evidence of poorer adaptive immunity is seen in people aged 50 to 60 with thymic demise, telomeric erosion in CD4 and CD8 T cells, decline in CD8 naive and central memory T cells, and oligoclonal expansion in the CD8 memory T cell compartment that parallels the nonhuman primate studies outlined. Although individuals aged 60 to 74 still have a reasonable ability to respond to a diverse array of pathogens because of a broad group of naive CD4 T cells[30] and normal induction of early activation markers in CD4 T cells, reduced proliferative capacity of naive T cells has been observed. The T cells are characteristic of activation-induced signatures that feature overexpression of zinc-induced genes (metallothioneins) and lack of a type I interferon signature.[31] A stable compartment of CD4 memory T cells remains, but there is accumulation of end-stage effector CD8 T cells, loss of the co-stimulatory protein CD28 on CD8 memory T cells, and gain of negative regulatory receptors on CD8 memory T cells.[28]

Naive CD4 and CD8 T cell compartments are characteristically greatly reduced after age 75, as is the repertoire of naive CD4 T cells. Furthermore, poorer responsiveness to T cell receptor stimuli with defects in proximal signaling, less induction of activation markers, a contracted repertoire of memory CD4 T cells, a predominance of end-stage

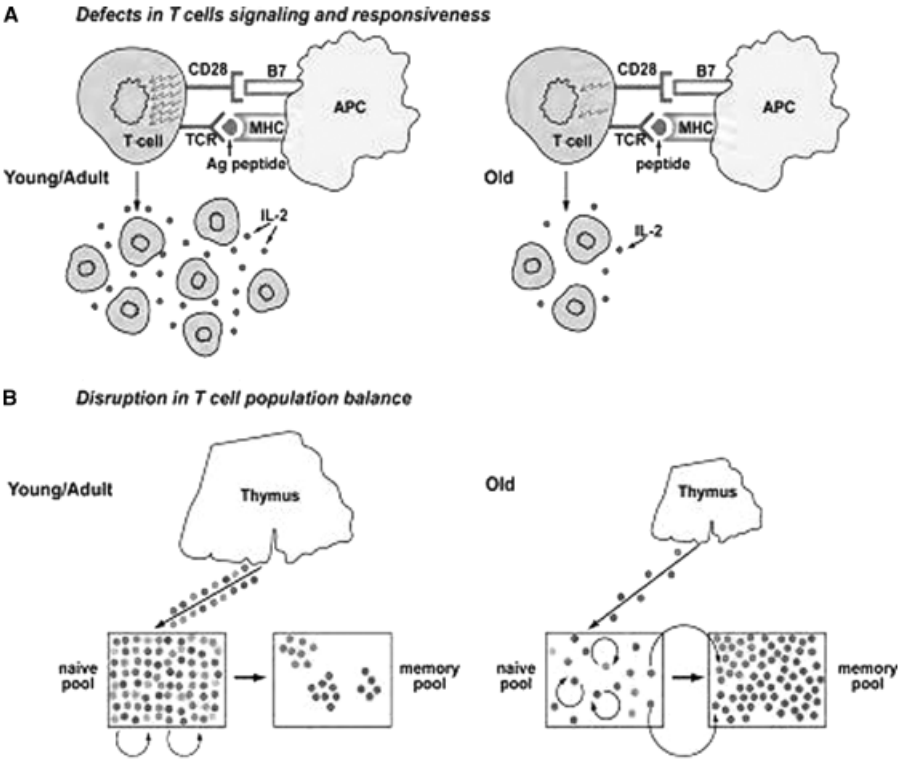

Figure 1. Conceptual models of age-related changes in T cell–dendritic cell interactions and T cell replication in older adults (A) and lower production of the full diversity of the naive T cell repertoire (B). (A) Aging results in less signaling between antigen-presenting cells and T cells, along with less interleukin-2 production, that may underlie impaired T cell proliferation. (B) Thymic involution and greater homeostatic cycling within the naive T cell pool have been shown and may be a cause of less T cell diversity noted with older age. Reprinted with permission.[26]

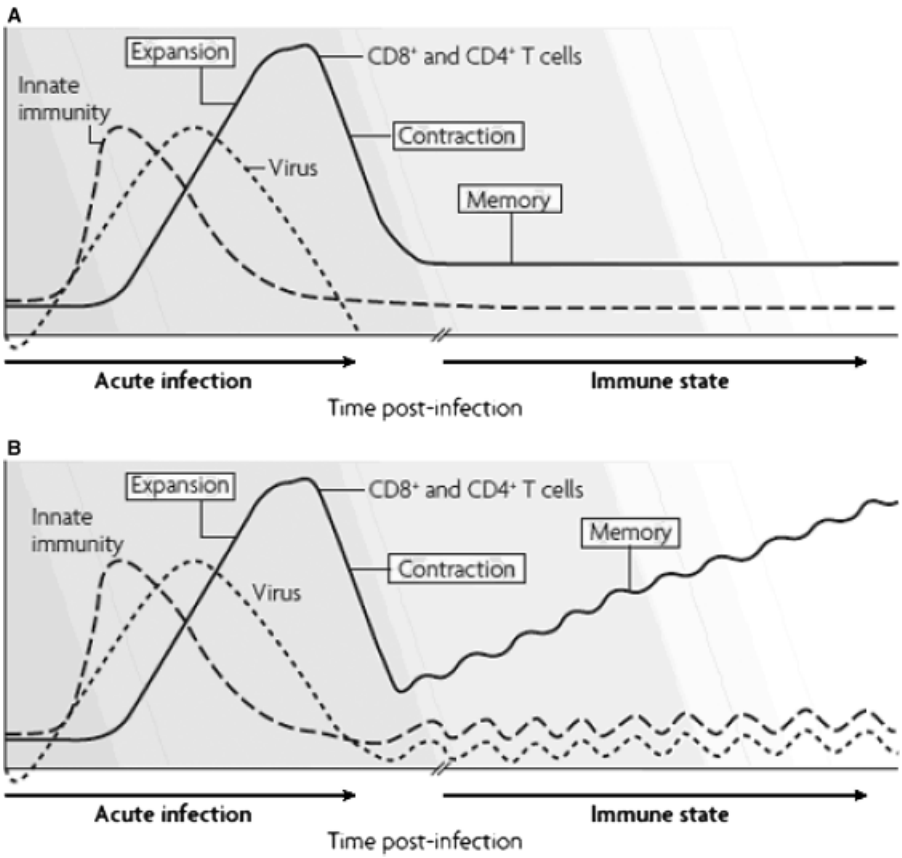

Figure 2. Immune response after acute (A) or chronic (B) viral infection. Acute viral infection results in limited expansion of immune cells, viral clearance, and contraction of effector immune cells resulting in a stable memory compartment. Chronic viral infections follow a similar early course but persist or reactivate, causing eventual expansion of a small number of clonal effector cells. These oligoclonal, senescent T cells overproduce cytokine and suppress immune responses to new antigens. Reprinted[26] with permission.

effector CD8 T cells, and high expression of negative regulatory receptors (e.g., CD85j, killer cell Ig-like receptors, and programmed death-1 (PD-1))[32,33] are all characteristics of the immune response of people aged 75 and older.

B Cells and Adaptive Immunity

B cell changes with age have also been examined in multiple animal and human models. B cell proliferation does not decrease in older mice, but there are reduced antigen-naive and expanded antigen-experienced pools and a smaller antibody repertoire with age. In mice, reduced efficiency in class switching (e.g., from IgM to IgG) to produce high-affinity antibodies is apparent with age; this process requires activation-induced adenosine deaminase and transcription factor E47, both of which are reduced in aged B cells.

Dramatically greater rates of pneumonia and bacteremia due to encapsulated organisms that require antibody production for clearance, B cell lymphomas, greater autoimmune disease, and less proliferation to mitogens, with a larger memory B cell population but smaller naive B cell repertoire suggest changes in B cell function in humans aged 75 and older. Unlike in mice, the numbers of circulating human B cells decline gradually over the age of 60, although a direct cause-and-effect relationship between human B cell decline and the greater incidence of invasive pneumococcal disease in adults aged 50 and older, rather than other aspects of immune senescence or inherent defects resulting from concomitant underlying disease, has not been established. A comparison of immune parameters and in vitro and in vivo immune responses in healthy older persons (mean age 80) and healthy younger adults (physician trainees with a mean age of 30) found similar results in both groups. Both groups showed vigorous responses to protein and polysaccharide vaccines,[34] suggesting that age alone could have a limited role in B cell dysfunction in the absence of substantial comorbidity.

HYPOTHETICAL MECHANISMS OF IMMUNE SENESCENCE

Oligoclonal Expansion of Inhibitory CD8+ T Cells

A possible contributing factor to the accumulation of senescent CD8+ T cells that inhibit vaccine and other immune responses is the presence of chronic infections such as CMV. Unlike acute infection that is resolved and provides limited support to T and B cell responses, persistent viral infections lead to frequent reactivation of immune responses and the accumulation of oligoclonal CD8+ cells over time (Figure 2). These oligoclonal CD8+ T cells have less proliferation but produce high levels of immune inhibitory cytokines. CMV seropositivity and expansion of oligoclonal, inhibitory CD8+T cells are characteristics of

the immune-senescent phenotype in humans, which is highly correlated with impaired vaccine responses.[27,28]

Age-Associated Accumulation of Inhibitory Proteins on the Cell Surface

Overexpression of inhibitory receptors, including PD-1 receptor and the killer cell lectin-like receptor G1, are seen in older mice, but their role in poor vaccine responses is unknown.[35] In chronic viral infections (e.g., human immunodeficiency virus (HIV), hepatitis C), PD-1 negatively regulates CD8 T cell responses, and PD-1 blockade reinvigorates immune responses against those viruses in mice (unpublished data).

Reductions in Telomere Length

Telomeres are essential for chromosomal integrity and completion of chromosomal replication and may play a critical role in regulation of the replicative life span of cells.[36] Shorter telomere length in human lymphocytes with cell division in vitro and with age in vivo has been observed gradually with increasing age.[37,38] Although senescent lymphocytes are associated with shorter telomeres, longer telomere length often is associated with greater replicative lifespan of lymphocytes in vitro.[39] Despite these findings, whether telomere erosion plays a causal role in age-associated immune function decline remains to be determined.

EFFICACY OF CURRENTLY RECOMMENDED VACCINES IN OLDER ADULTS

The Centers for Disease Control and Prevention's (CDC's) Advisory Committee on Immunization Practices, a committee comprising vaccine experts that develops public health recommendations for vaccine administration and recommends a number of vaccines for adults based on age (Figure 3). These recommendations are updated as needed. At this workshop, the efficacy of influenza, pneumococcal polysaccharide, and zoster vaccines was discussed; each is briefly reviewed below. More-extensive reviews of the individual vaccines are widely available in the published literature.

Influenza

Influenza is one of the top 10 causes of death in older adults.[40] Individuals aged 65 and older are at high risk for serious influenza-associated illness, and complications are responsible for up to 10% of winter cardiopulmonary deaths. An estimated 10% of annual pneumonia and influenza deaths and 3% of all respiratory and circulatory deaths are attributed to influenza, with 90% of these deaths occurring in those aged 65 and older. A review of 31 studies found that influenza vaccination had 50% to 80% efficacy in preventing influenza illness in healthy adults, with highest efficacy in years with a good match between vaccine and circulating strains,[41] but the efficacy of influenza vaccines in adults aged 65 and older and persons with chronic diseases of the heart, lungs, and kidneys is a subject of intense controversy. One clinical trial of healthy community dwelling adults aged 60 and older reported vaccine efficacy of 60% against laboratory-confirmed influenza, but there are no clinical trials involving frail elderly persons and outcomes of hospitalization or death. Some evidence indicates that the antibody response to vaccination decreases with age.[42]

Most studies of vaccine effectiveness in older persons have used observational data. There is considerable debate about the interpretation of studies that have used large administrative data and outcomes such as hospitalization or deaths from pneumonia and influenza. Although some studies suggest large decreases in hospitalizations and deaths due to influenza vaccine, annual estimated influenza-associated mortality has changed little over the last 2 decades, despite large increases in vaccine uptake.[43] In addition, analysis of hospitalized elderly persons has revealed marked differences in functional status between those who were and were not immunized with influenza vaccine that probably resulted in overestimation of vaccine efficacy.[8] To try to address some of these concerns, the CDC has begun a cooperative group study to examine annual vaccine effectiveness using a case–control design and medically attended

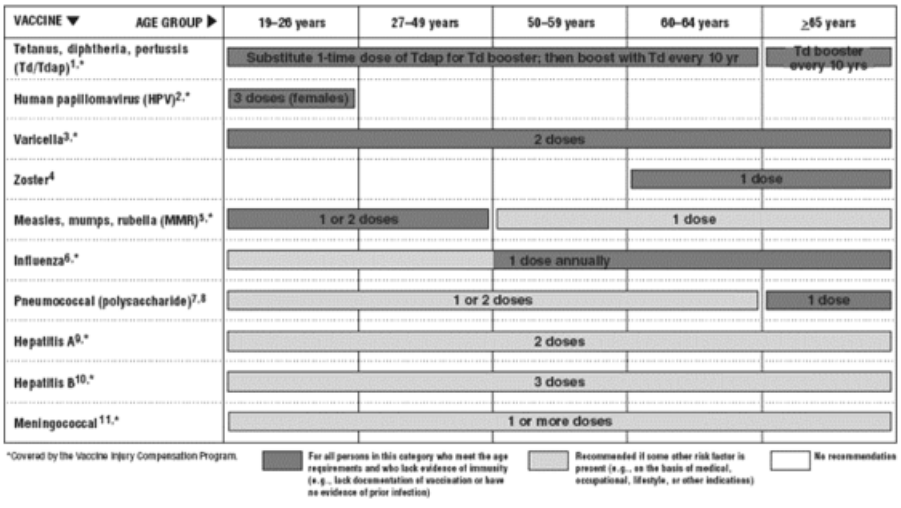

Figure 3. Centers for Disease Control and Prevention recommended adult immunization schedule according to vaccine and age group—United States 2009. Source: http://www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm.

illness as the outcome. In the meantime, the official CDC recommendation remains annual provision of influenza vaccine to all adults aged 50 and older and all those likely to transmit influenza to vulnerable older adults (e.g., family members, close contacts, healthcare workers, and nursing home staff). Known risks of the influenza vaccine are local pain and a mild fever or a feeling of malaise.

Pneumococcal Polysaccharide Vaccine

Adults aged 65 and older are at high risk for pneumococcal disease. Observational studies of pneumococcal polysaccharide vaccine (PPV) in older adults have consistently demonstrated a lower risk of invasive pneumococcal disease (IPD), defined according to positive blood cultures, in older adults with no immune-suppressive drugs or disease (e.g., lymphoma) who receive PPV, but the efficacy in immunocompromised hosts is less convincing.[44–51] One case–control study examined time since immunization in different age groups and found a trend toward less efficacy with older age (≥65) and time since vaccination.[44] CDC recommends a single immunization after age 65 (Figure 3). This recommendation is based on evidence of waning efficacy of PPV in people aged 85 and older and some evidence in the literature that antibody responses are not boosted, and are perhaps even blunted, with repeated dosing of PPV.[45] There are some preliminary data that suggest that the antibody response to pneumococcal conjugate vaccine, which is protein-linked, may be greater than the antibody response to the current PPV in older adults.[52]

The efficacy of PPV for outcomes other than IPD in older adults is uncertain. Clinical trials have not consistently demonstrated a reduction in all-cause pneumonia with PPV in adults aged 65 and older, perhaps because of the many other causes of community-acquired pneumonia, and it is generally believed that PPV does not reduce the risk of nonbacteremic pneumococcal pneumonia.[53–55] Studies are needed to determine whether pneumococcal conjugate vaccines can prevent nonbacteremic pneumococcal pneumonia, which is much more common than IPD. A randomized trial of a 13-valent conjugated pneumococcal vaccine against PPV to prevent vaccine-type pneumococcal pneumonia is under way in 85,000 older adults in the Netherlands.[56] Current side effects of PPV23 include mild redness or pain where the vaccine was given, fever, and muscle aches, with more-severe local reactions in less than 1% of those vaccinated.

Zoster

The CDC also recommends vaccination against herpes zoster, or shingles, a disease caused by reactivation and multiplication of endogenous, latent varicella-zoster virus (VZV) (Figure 3). Although the varicella vaccine against chickenpox, usually administered to children before primary infection, has efficacy of 95% or greater and induces herd immunity,[57] vaccination against VZV in persons after primary infection and prevention of zoster requires changing the host–virus relationship rather than preventing primary infection. Cell-mediated immunity is the major determinant of the incidence and severity of herpes zoster. Levels of cell-mediated immunity decline with advancing age, corresponding with an age-related increase in the incidence and severity of shingles, but levels of antibody to VZV do not decline.[58]

The zoster vaccine, a live-virus vaccine, boosts the declining level of preexisting cell-mediated immunity to the virus, reducing the frequency and severity of shingles in older adults. Studies of vaccine efficacy found burden of illness, an overall measure of pain over time, was 65.5% lower in individuals aged 60 to 69 and 55.4% lower in those aged 70 and older. Pain that interfered with ADLs and postherpetic neuralgia (PHN) was approximately two-thirds less after vaccination.[57] Incidence of disease 63.9% less in the people aged 60 to 69 but only 37.6% less in those aged 70 and older, whereas efficacy for PHN was preserved with age and did not differ in the two groups.[58]

In addition to the CDC-recommended vaccinations mentioned above, it is also recommended that adults aged 65 and older receive a tetanus booster shot every 10 years.

POTENTIAL FOR VACCINES DIRECTED AGAINST PROBLEM ORGANISMS IN OLDER ADULTS

Clostridium difficile

Most people are exposed to *Clostridium difficile*; many do not develop infection or symptomatic illness, but rates of *C. difficile* disease in hospitalized patients tripled from 2000 to 2005, with the increase almost exclusively in adults aged 65 and older[59] (Figure 4). *C. difficile*–related deaths more than quadrupled in the United States from 1999 to 2004, and nearly all deaths occur in older adults. *C. difficile*–attributable death rates were four times those of methicillin-resistant *Staphylococcus aureus* (MRSA) and six times those of all other intestinal infectious diseases combined.[59] Nonantibiotic approaches to this antibiotic-induced disease are sorely needed.

Several *C. difficile* toxins have been characterized, and toxins A and B both result in diarrhea and colitis.[60] Evidence for protective immunity is seen in the fact that approximately two-thirds of the population has antitoxin antibodies, which appear to be acquired early and main-

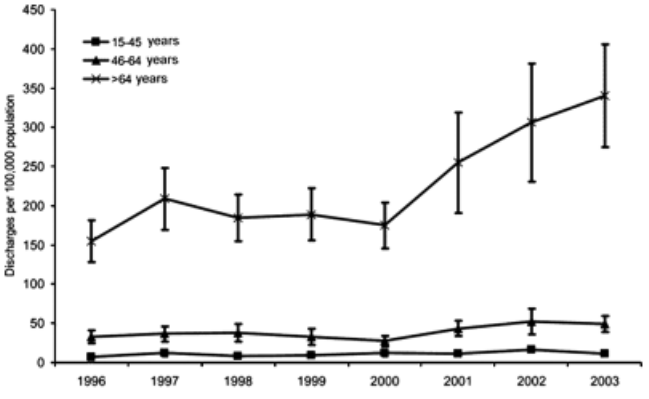

Figure 4. Rates of U.S. short-stay hospital discharges with *Clostridium difficile* listed as any diagnosis by age. Reprinted from McDonald LC, Owings M, Jernigan DB. *Clostridium difficile* infection in patients discharged from US short-stay hospitals, 1996–2003. Emerg Infect Dis [serial on the Internet]. 2006 Mar [May 15, 2009]. Available at http://www.cdc.gov/ncidod/EID/vol12no03/05-1064.htm with permission.[58]

tained throughout life. Serum IgG anti-toxin A levels are high in asymptomatic carriers. Recurrent infection is common, and antibiotic therapy with metronidazole or vancomycin may perpetuate vulnerability to recurrent infection, especially in those with a defective immune response.[60] Antitoxin antibody levels are lower in those with recurrent symptoms; conversely, higher levels are associated with lower risk for recurrent diarrhea.[61] Active and passive immunity are both possible. Some promising data from early studies using toxoid vaccine demonstrate strong antibody responses,[62] but larger controlled trials, particularly in older adults with significant comorbidity, are needed.

Streptococcus agalactiae

Infection due to *Streptococcus agalactiae*, previously known as Group B streptococcus (GBS), is most commonly associated with disease in neonates due to maternal–fetal transmission, but a substantial disease burden has also been documented in adults aged 65 and older.[63] Adults aged 65 and older have a rate of GBS infection five times as great as those aged 15 to 64. The case-fatality rate for invasive GBS in adults aged 65 and older is 9% to 10%, and 50% of all invasive GBS-associated deaths occurred in this age group. The incidence of invasive GBS disease in nonpregnant adults increased 32% from 1999 to 2005, with more than 16,000 cases and 1,140 deaths in 2007 and an unknown but much larger number of skin and soft-tissue infections. Nearly all GBS infections in adults occur in persons with underlying illness—most often diabetes mellitus, heart disease, or malignancy. Serotype distribution differs according to age, with type V prevalent in older adults and type III in newborns.[63]

A five-valent GBS conjugate vaccine theoretically could prevent approximately 85% of invasive GBS disease in adults. A number of candidate GBS conjugate vaccines are in trials and have been found to elicit more than fourfold increases in serum capsular polysaccharide-specific IgG in 80% to 100% of healthy adults younger than 50, including two type V vaccines.[64] One vaccine, a tetanus-toxoid-linked GBS serotype V conjugate, resulted in a fourfold rise in serum antibody titers in 76% of healthy older adults.[65] Limited published data suggest that the GBS vaccines tested to date are well tolerated.

Methicillin-Resistant *Staphylococcus aureus*

MRSA is a ubiquitous pathogen that can cause a broad range of clinical conditions, including skin infection, pneumonia, and bacteremia. The rate of MRSA hospitalization was three times as high in adults aged 65 and older as in any age group.[66] Immunity to *S. aureus* infections is characterized by high innate resistance to invasive staphylococcal infection due to epidermal and mucosal surface barriers and intact cellular, humoral, and innate immune host defenses. Although serious infection has usually been dependent on mechanical, immunological, and metabolic changes in host status and most often seen in the past in healthcare settings, community-associated MRSA is becoming increasingly common.[67]

With no good evidence to suggest a clear mechanism of immunity, there is no guidance on how to make a vaccine against MRSA. Patients who recover from *S. aureus* infections are not immune and are at higher risk for re-infection; thus, the typical immune response to *S. aureus* cannot be expected to induce protective immunity. A logical approach might be to target the cell-surface polysaccharides and capsules that prevent opsonic killing by phagocytes, but clinical trials of capsule vaccines have been unsuccessful, although preclinical studies have shown that several vaccine candidates to altered or normally concealed components of the bacteria can induce protection from infection and serious disease. For example, poly-N-acetyl β-1-6-glucosamine (PNAG) is a surface polysaccharide on almost all strains of *S. aureus*. Antibodies against a chemically modified version of PNAG, prepared by reducing the level of N-acetylation (deacetylated PNAG or dPNAG), had efficacy in a few animal models.[68] In addition, a fully human monoclonal antibody that can bind to native and dPNAG is opsonic against a variety of *Staphylococcal* strains and improves survival in a mouse model of lethal infection.[69]

Despite the difficulties in developing an effective *S. aureus* vaccine, two current candidate vaccines target surface proteins of *S. aureus* in clinical trials. One product, used for passive immunization, is a humanized monoclonal antibody directed at lipoteichoic acid, a component of the *S. aureus* cell wall; that compound has been examined only in clinical trials enrolling neonates. The other candidate is a vaccine for active immunization, V710, that targets iron surface determinant B of *S. aureus*, induces strong antibody responses in nonhuman primates,[70] and is now being used in a phase II clinical trial to reduce the risk of postoperative complications in patients undergoing cardiothoracic surgery.

NEW APPROACHES TO BOOST VACCINE RESPONSES IN OLDER ADULTS

Greater Antigen Dose Including Baculovirus-Expressed Antigens

Although numerous studies of inactivated influenza vaccines demonstrate greater antibody responses with greater dosage, few of these studies have included older adults; one study in the 1960s, which was conducted in a retirement community, suggested greater efficacy with a high-dose vaccine.[71] More-recent work with influenza vaccine in an older population has determined that greater vaccine antigen dose results in greater serum antibody responses, mucosal antibody responses, and antibody responses to related potential future influenza virus variants. Greater injection site reactions were also noted but were modest.[72]

Greater antigen dose is difficult with the current vaccine or manufacturing process because it would require a much greater capacity. A more-economical and -practical way to produce high-dose vaccines would be to use influenza component (hemagglutinin (HA) and neuraminidase) vaccines derived using highly efficient processes. Baculovirus-derived vaccines, or vaccines grown in Baculovirus, against influenza have been evaluated widely, including in studies in older adults with antigen doses up to nearly 10 times as high as HA or neuraminidase present in the current vaccine.[73–77] Recombinant HA appears to be well tolerated and immunogenic, inducing a functional antibody, and protective efficacy has been demonstrated in healthy adults at levels similar to those of other inactivated influenza

vaccines. Higher HA doses can result in higher titer antibody responses in older adults. Baculovirus is used to infect insect cells to produce the proteins; the technology is already in use for human vaccines, and efficient protein production allows greater supply with easy scale-up that does not require specialized facilities, and the substrate does not select receptor variants. The use of insect cells may further reduce the risk of egg-associated allergic reactions infrequently encountered with the current vaccine, although because the correlates of vaccine protection (laboratory markers of immune response that accurately predict protection from disease) are not well defined in older adults, particularly those with comorbidity, it is difficult to definitively determine which subunits to include and subunit vaccines stimulate whether the most-protective immune responses.

TLR Agonists

TLR expressed by various immune cells, including DCs and other APCs, recognize microbial substances. TLR agonist binding results in activation of innate immunity, which in turn can enhance adaptive immunity. Some TLR agonists (TLR3, TLR4, TLR5, TLR7/8, TLR9) have shown promise as vaccine adjuvants. Better responses might be possible by combining two or more immune modulators that act synergistically through different pathways or on different cells (e.g., TLR4+TLR9), or provide physiochemical advantages for delivering a stimulatory signal (e.g., alum+TLR agonist) (Table 1).

CpG-oligodeoxynucleotide (CpG-ODN), a TLR9 agonist, in combination with alum, has been shown to be a highly effective adjuvant to several different antigens in young healthy adults. Various data—including effectiveness in older mice and immune-compromised (low CD4+T cell count) HIV-positive patients—suggest that CpG also might be effective in older adulst as an influenza vaccine adjuvant. Defective CD4+ T cells play an important role in age-related decline in adaptive immunity,[78] CD4+ T cells from young adult mice restore IgG responses when transferred into aged mice,[79] and inflammatory cytokines in vivo enhance defective CD4+ T cell function in older mice.[80] Murine studies have shown lower TLR expression and function in older animals,[81] but other studies substantiate the ability of CpG-ODN to restore antitumor responses in older mice.[82] A number of other studies have validated the effect with different forms of antigen.[83–87] It appears that matching a TLR to a specific pathogen is not required because there is considerable redundancy in these systems.

Thirty-seven, mostly phase I, published clinical trials have tested CPG 7909 as an adjuvant, and strong augmentation of antibody responses has been noted with a variety of antigens; none of these trials were performed in older humans (≥65). Enhanced T cell immunity has been demonstrated with melanoma[88] and hepatitis B virus vaccines[89] in young adults. Furthermore, trials in healthy or HIV-infected adults showed that CpG enhanced antibody responses with a commercial hepatitis B vaccine. Hepatitis B antigen responses decline dramatically with age, starting at approximately age 35.[90] Trials of CpG-adjuvanted hepatitis B vaccine could be tested in older adults as a proof of concept for use of this novel adjuvant to improve immunogenicity of other vaccines in the elderly.

Mucosal Targeting

The majority of pathogens enter the body through mucosal tissues, with two major routes for induction of mucosal immune responses: gut-associated lymphoid tissue (GALT) and nasal-associated lymphoid tissue (NALT). Studies in mice demonstrate that NALT is preserved well into older age and that delivering adjuvanted vaccine preparations through the intranasal route is effective.[91,92] A combination of adjuvants was most effective and enhanced ovalbumin-specific antibody response (plasma IgG and IgA and secreted IgA) and upregulated Th1- and Th2-type cytokine production.

Blocking Inhibitory Receptors

T cell changes in older mice include more negative regulators of T cell function, such as high expression of PD-1 receptor and KLRG1 on T cells.[93] There are also changes with age in negative regulatory pathways in humans, but the precise connection between inhibitory pathways and immunity is not clear. Blocking negative regulatory pathways could provide opportunities to manipulate the quality of immunity in older people, and investigators are examining in vivo manipulation and depletion of Treg and

Table 1. Adjuvants Used to Enhance Vaccine Efficacy and the Immune Responses Augmented by Each Adjuvant*

Adjuvant	Antibody	CD4+ Interferon-Gamma Secretion	CD8+ Cytotoxic T Lymphocytes Determined According to Chromium Release Assay
CpG	++	+	++
Aluminum hydroxide	+	–	–(+)
CpG+aluminum hydroxide	+++++	++	++++
Lipid emulsions	++	–	++
CpG+lipids	++++	++++	+++
Saponin	++	–	++
CpG+saponin	+++	++++	+++
ISCOMS	+++++	+	+++
CpG+ISCOMS	+++++	+++++	+++

* + and – indicate degree of enhancement of response in mice over antigen alone when administered through the intramuscular route. Results derived with various antigens and adjuvants were used to assign these general trends, which do not necessarily represent a given adjuvant or delivery system.
CpG = cytosine and guanine; ISCOMS = immune-stimulating complexes.

blockade of inhibitory receptor pathways in vivo (unpublished data). Because blockade of the PD-1 pathway has therapeutic benefits in other settings,[94,95] testing the effect of targeting this pathway in older mice is of potential interest.

CHALLENGES IN TRANSLATION OF NEW VACCINES TO CLINICAL USE

The controlled conditions of animal models often fail to translate to human communities. Important clinical outcomes in older persons (e.g., inflammatory measures, thrombotic complications, functional assessments, catastrophic disability) are not typically measured and must be included in future studies. Longitudinal studies of immune memory are needed to determine optimal timing of vaccine administration (young adulthood, middle age, advanced age?) to provide optimal protection in old age. A mixed-effects model, a model used with dependent data, which examines a group or cluster of people over a course of many years investigating the fixed and random effects, may be the best way to achieve some uniformity in future studies.

An additional difficulty in developing vaccines in adult populations is performing vaccine efficacy studies in older adults. Although the overall burden of disease is high because of the large numbers of older adults, the incidence of disease is usually low, necessitating large, expensive trials.

The challenges of optimizing immunization for older persons are important to public health and public policy. Although pediatric immunization has been a spectacular success (95%) built on a public–private partnership, only a modest proportion (50–70%) of adult target populations are immunized, with disparities according to income, race, and ethnicity. Funding is a critical issue, with 30 million to 40 million adults without medical insurance and others who face the barriers of copayments and other out-of-pocket expenses. In addition, a public health perspective may suggest that immunizing groups capable of transmission of disease to vulnerable seniors (seniors with multiple comorbidities) will be more effective than immunizing seniors with limited immune response capacity, but this needs to be tested in well-conducted trials.

PRIORITIES AND QUESTIONS FOR FUTURE RESEARCH

General Questions

- At what age(s) do specific vaccines demonstrate waning efficacy, and how does the diversity of the older population affect immunity? What is the interaction between age and functional status on the efficacy of a vaccine?
- Given age-related declines in immunity and nascent evidence of long-lived immunity for many vaccines (e.g., smallpox), at what younger stages of the life can and should immunization be provided to have the greatest effect on disease in older ages? What are the effects of multiple vaccines over time?
- What are predictors or surrogate markers of vaccine efficacy and failure, including the role of specific nutritional deficiencies and genetics?
- What are the best means for measuring vaccine efficacy in very frail adults?

Mechanisms

- What are the relative contributions of DC, T cell, and B cell deficits in immune senescence? Are there common factors (e.g., extrinsic influences) that cause these defects, or are they cell specific (e.g., intrinsic)?
- What are the roles of chronic viral infection, inhibitory cell surface markers, suppression by exhausted CD8 cells, and upregulation of other negative responses? Are the deficits fixed or reversible?
- Are abundant Tregs a matter in age-related nonresponse to vaccines? Are Treg quantity and quality results of aging or comorbidity?
- Are there common mechanisms of immune exhaustion, such as naive T cell overreplication or stem cell exhaustion?
- Can boosting the innate immune system overcome T cell and B cell deficits in humans?
- Are new adjuvants or delivery vehicles (e.g., TLR agonists) and combinations useful in older adults, as shown for murine models of immune senescence?
- What is the role of greater antigen? How much antigen is needed to be effective while limiting reactogenicity? Why does it work for some components and not others, and what is the duration of response?
- How can other modalities of enhancing response or reducing age-related inhibition (e.g., mucosal targeting, blocking inhibitory receptors) be used and combined with adjuvants and delivery vehicles?

Enhancing Available Cohorts and Resources

- What additional databases are available to determine correlates of protection, surrogate markers of nonresponse, and duration of response (i.e., can longitudinal aging studies answer these questions)? Many were initiated before more-sophisticated immune response measures were known but could provide populations for current study of older adults.
- Can longitudinal cohorts of men and women returning from military service, who have received a variety of vaccines, be useful to study kinetics of antibody and immune decline to investigate appropriate timing of vaccines?
- How can animal models be developed to mirror human conditions (e.g., repeated influenza infection) rather than studying only primary infection? What are the most-representative functional assessments in older animals that reflect functional status in humans? What nondeath outcomes can be represented in animal models that might be important in older humans?

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