



CME review article

Adult immunizations: updates and practical guidance for the practicing allergist-immunologist

Jeremy M. Sikora, MD, and Michael S. Tankersley, MD

Division of Allergy and Immunology, Department of Medicine, Wilford Hall Medical Center, San Antonio, Texas.

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- Discuss updated adult vaccine recommendations, rationale supporting these recommendations, and methods to maintain currency.

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Planning Committee Members:

Jeremy M. Sikora, MD (Senior Author)

Michael S. Tankersley, MD (Author)

Gailen D. Marshall, Jr, MD, PhD (Editor-in-Chief)

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Introduction

For the practicing allergist-immunologist, advocating for optimal patient immunization is a uniquely challenging aspect of clinical

care. Physicians are confronted with multiple systemic barriers, including cost concerns, patient misperceptions, poor multiple-dose vaccine series compliance, and disparities in vaccine access.^{1–4} Beyond these barriers, however, physician-imposed barriers

Requests for reprints should be addressed to: Jeremy M. Sikora, MD, Allergy and Immunology Division, Department of Medicine, Wilford Hall Medical Center, 2200 Bergquist Dr, Ste 1, Lackland Air Force Base, San Antonio, TX 78236 E-mail: jeremy.sikora@us.af.mil

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Table 1
ACIP-Recommended Routine Adult Immunization Schedule based on age (independent of risk factors)^a

Age group, y	Vaccine							
19–21	MCV4 ^{b,c}	HPV ^d	TIV/LAIV ^f	Td/Tdap ^h	Varicella ⁱ	MMR ^j	m	p
22–26	c	HPV ^{d,e}	TIV/LAIV ^f	Td/Tdap ^h	Varicella ⁱ	MMR ^j	m	p
27–49	c		TIV/LAIV ^f	Td/Tdap ^h	Varicella ⁱ	MMR ^j	m	p
50–59	c		TIV	Td/Tdap ^h	Varicella ⁱ	MMR ^j	k	m,n
60–64	c		TIV	Td/Tdap ^h	Varicella ⁱ	MMR ^j	Zoster ^l	m,n
≥65	c		TIV ^g	Td/Tdap ^h	Varicella ⁱ	MMR ^j	Zoster ^l	PPSV23 ^o

Abbreviations: ACIP, Advisory Committee on Immunization Practices; HPV, human papillomavirus [vaccine]; LAIV, live attenuated influenza vaccine; MCV4, meningococcal conjugate vaccine quadrivalent; MMR, measles-mumps-rubella [vaccine]; PPSV23, 23-valent pneumococcal polysaccharide vaccine; Td, tetanus/reduced diphtheria toxoid [vaccine]; Tdap, tetanus/reduced diphtheria toxoid and acellular pertussis [vaccine]; TIV, trivalent inactivated influenza vaccine.

^aAdapted with permission from the ACIP's Recommended Immunization Schedule, US 2012,¹¹ which contains a list of vaccine contraindications.

^bA single dose of MCV4 is indicated in military recruits and first-year college students living in residence halls up to 21 years of age if they have not received a dose on or after their 16th birthday.

^cConsider meningococcal vaccination in high-risk adults (Table 2).

^dThree-dose series of either quadrivalent (HPV4) or bivalent (HPV2) HPV vaccine. For males, HPV4 series only; for females, either HPV4 or HPV2 series.

^eHPV vaccine series should be administered to all women aged 22 to 26 years, if not previously vaccinated. Vaccination of males in this age group on with high-risk indicators (Table 2).

^fAnnual influenza vaccination is recommended in all adults, TIV for adults of all ages, and LAIV for adults aged 19 to 49 years without a contraindication.

^gAdults 65 years or older can receive standard-dose TIV or high-dose TIV (Fluzone High-Dose).

^hTd booster every 10 years, substituted with Tdap once (given regardless of interval since preceding Td booster).

ⁱTwo total varicella vaccine doses, administered 4 to 8 weeks apart in individuals without evidence of immunity.

^jAll adults born in or after 1957 should be immunized with MMR (1 or 2 doses); adults born before 1957 are considered immune.

^kZoster vaccine is licensed for administration in individuals aged 50 to 59 years; however, there is currently no ACIP recommendation for routine immunization in this age group.

^lSingle zoster vaccine dose, without booster.

^mConsider PPSV23 immunization in high-risk adults younger than 65 years (Table 2).

ⁿPPSV23 vaccination may be considered by public health officials in American Indians and Alaska natives aged 50 to 64 years living in areas of increased risk of invasive pneumococcal disease.

^oOnly 1 PPSV23 dose is indicated in patients who receive their first dose at 65 years or older.

^pConsider hepatitis A and hepatitis B vaccination in high-risk adults (Table 2).

ers exist. Rapidly evolving advances in preventive medicine contribute to a perception that immunization proficiency is unattainable. Furthermore, vaccination schedule complexity can make it seem that time-efficient counseling is simply impractical in a busy practice.

Evidence suggests that physicians are missing opportunities to provide immunization education. Recent published survey data indicated that only 41% of health care professionals strongly recommended zoster vaccination when indicated.² Missed opportunities exist in notably high-risk populations as well. Kotsanas et al⁵ demonstrated a significant difference in the likelihood of immunization education and vaccination in postsplenectomy patients, depending on the indication for splenectomy.⁵ In addition, published survey data collected from patients of a US university-based outpatient cancer treatment clinic indicate that 33% of patients reported never receiving influenza vaccination, 30% of patients older than 65 years reported never receiving pneumococcal vaccine, and only 7% of patients reported receiving vaccination counseling by their oncologist.⁶ Missed opportunities are not without consequence. In fact, although vaccine efficacy varies, depending on age, health status, and vaccine-specific responsiveness, data published in 2003 indicate that approximately 45,000 adults die each year from vaccine-preventable disease.⁷

However, evidence indicates that physician immunization recommendations are a significant predictor of vaccine regimen adherence.³ A systematic literature review by the US Task Force on Community Preventive Services identified strong evidence that simple physician to patient reminder or recall interventions are effective in improving vaccination rates.⁸ By simply identifying and reminding patients of indicated vaccinations, practicing allergists-immunologists have the potential to enhance vaccination compliance rates, which is particularly vital to the care of high-risk patients.

Immunization opportunities and implications permeate the field of allergy-immunology, most notably in the areas of asthma management and immunodeficiency, including assessments of

immune responsiveness. Suboptimal adult immunization rates, overlaid on evidence of the positive effect of physician-driven immunization counseling, provide a powerful dictate for allergists-immunologists to seek a more active role in immunization advocacy in the clinical setting.

As noted, immunization-specific information is quickly evolving and ever-accumulating. This article reviews recent immunization-specific updates and vaccine-specific guidance, as they apply to the practicing allergist-immunologist, and provides evidence in support of the importance of the allergist-immunologist's role in immunization advocacy. The MEDLINE and OVID databases were used to identify relevant articles using the following keywords: *immunization, vaccination, compliance, barriers, rates, Tdap, pertussis, HPV, cervical cancer, genital warts, papillomatosis, pneumococcal, conjugate, polysaccharide, asthma, smoking, varicella, zoster, asplenia, hepatitis B, hemodialysis, and HIV*. References from the chosen articles were also examined. Articles were chosen based on their relevance and currency with regard to the subject matter.

This article is not meant to represent a comprehensive review of adult immunization but rather to serve as a practical reference for physicians, targeting recent updates and common immunization issues presented to the practicing allergist-immunologist. The scope of this article does not encompass an in-depth discussion of relatively unvaried guidance, as in adult measles-mumps-rubella (MMR) vaccination, or regularly adapted recommendations concerning annual influenza vaccination. However, Tables 1 and 2 were constructed referencing Advisory Committee on Immunization Practices (ACIP) recommendations for adult vaccination in an effort to provide a high-yield, concise reference for clinical application, with footnotes highlighting critical vaccine-specific details. Furthermore, the "Practical References" section at the end of this article provides practical guidance on efficient access to additional targeted adult immunization information. It is important to note the difference between ACIP recommendations and Food and Drug Administration (FDA) indications. Although the ACIP recommendations frequently parallel the FDA indications, situations occur

Table 2
2012 ACIP-Recommended High-Risk Adult Immunization Schedule based on risk factors^a

Age group, y	Vaccine					
19–26	MCV4 ^b	HPV ^c	PPSV23 ^{d,e}	Hepatitis A ^g	Hepatitis B ^{h,i}	Hib ^j
27–55	MCV4 ^b		PPSV23 ^{d,e}	Hepatitis A ^g	Hepatitis B ^{h,i}	Hib ^j
≥56	MPSV4 ^b		PPSV23 ^{d,e,f}	Hepatitis A ^g	Hepatitis B ^{h,i}	Hib ^j

Abbreviations: ACIP, Advisory Committee on Immunization Practices; Hib = *Haemophilus influenzae* type B [vaccine]; HPV, human papillomavirus [vaccine]; MPSV4, meningococcal polysaccharide vaccine; MCV4, meningococcal conjugate vaccine quadrivalent; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

^aAdapted with permission from the ACIP's Recommended Immunization Schedule, United States 2012,¹¹ which contains a list of vaccine contraindications.

^bImmunize anyone with a meningococcal vaccine (conjugated vs polysaccharide based on age) with the following indications: 2 doses: anatomical or functional asplenia, persistent complement deficiency, human immunodeficiency virus (HIV); 1 dose: persons entering college through 21 years of age, military recruits, microbiologists with routine *Neisseria meningitidis* exposure, persons traveling to regions with endemic meningococcal exposure. Revaccination with MCV4 every 5 years for patients who remain at increased risk of infection (eg, functional/anatomical asplenia, complement deficiency).

^cRoutine HPV series immunization (Table 1). In addition, vaccinate males with immunocompromise, including those with HIV and men who have sex with men (MSM) aged 22 to 26 years with the quadrivalent vaccine (HPV4).

^dImmunize anyone with the PPSV23 with the following indications: medical: asplenia (functional or anatomic), chronic lung disease (including asthma), alcoholism, chronic heart disease (excluding hypertension), chronic liver disease or cirrhosis, diabetes mellitus, immunocompromise (including chronic renal failure or nephritic syndrome, malignant tumor, immunosuppressive therapy), immunodeficiency or HIV, cochlear implants, and cerebrospinal fluid leaks; other: persons who smoke cigarettes, residents of nursing homes or long term care facilities.

^eSingle booster dose 5 years after initial pneumococcal polysaccharide vaccine dose is indicated if first dose was administered at younger than 65 years.

^fPneumococcal polysaccharide vaccine is age indicated in all patients 65 years or older. No booster is indicated if first dose is received at 65 years or older.

^gImmunize anyone with hepatitis A virus (HAV) vaccine (2-dose series if administered as a single antigen vaccine, 3 doses if administered in a combination hepatitis A/B vaccine) with the following indications: behavioral: MSM, injectable drug use; occupational: persons working with HAV-infected primates or HAV research laboratory exposure; medical: chronic liver disease, persons who receive clotting factor concentrates; other: persons traveling to regions with intermediate or high endemic rates of HAV, also persons with anticipated close personal contact to such individuals resulting from international adoption.

^hImmunize anyone with hepatitis B virus (HBV) vaccine (3-dose series) with the following indications: behavioral: sexually active individuals (not in a long-term or mutually monogamous relationship, persons being evaluated or treated for sexually transmitted infection (STI), MSM, injectable drug use; occupational: health care personnel or public safety workers with potential for HBV-infected body fluid exposure; medical: patients with diabetes younger than 60 years, chronic liver disease, end stage renal disease (ESRD), including those who are hemodialysis-dependent, HIV infection; other: persons traveling to regions with intermediate or high endemic rates of HBV, household contacts or sexual partners of those with chronic HBV, clients and staff members in the following settings: developmental disability care facilities, HIV/STI treatment facilities, drug abuse treatment facilities, health care settings that treat MSM and injectable drug users, correctional facilities, ESRD/hemodialysis treatment facilities.

ⁱHemodialysis or immunocompromised patients should receive 1 of the 2 following alternate schedules: 1 dose of Recombivax HB (40 µg/mL per dose) at 0, 2 and 6 months OR 2 doses of Engerix-B (20 µg/mL per dose) at 0, 1, 2, and 6 months.

^jConsider 1 dose of Hib vaccine in those with anatomical or functional asplenia (including sickle cell disease), leukemia, or HIV if not previously immunized.

where the 2 are incongruent. In discussing vaccination recommendations, this article focuses on published ACIP guidance.

Vaccine-specific updates

Tdap immunization

The current adult recommendation for a 1-time dose of tetanus-diphtheria-acellular pertussis (Tdap) vaccination includes (1) any adult younger than 65 years, and (2) any adult 65 years and older with close infant (child less than 12 months) contact or interaction (Table 1). In addition, any adult 65 years or older (regardless of infant interaction) may receive a 1-time Tdap dose in place of a single tetanus-diphtheria (Td) immunization. Limited data are currently published on Tdap safety in this older age group; however, ACIP-reviewed unpublished Vaccine Adverse Event Reporting System data from 2005 to 2010 indicate acceptable vaccine risk. Currently, 2 Tdap vaccinations are available in the United States, namely, Adacel (Sanofi Pasteur, Swiftwater, Pennsylvania) and Boostrix (GlaxoSmithKline, London, England), both of which are acceptable for use in adults 65 years or older based on current ACIP recommendations.⁹

The impetus for adding the pertussis component stems from data regarding poor pertussis control in the United States. Specifically, data indicate an increase in pertussis incidence in 2009 relative to 2007–2008, with the highest reported rates in the age group of greatest risk, namely, infants younger than 6 months (127 per 100,000 cases).¹⁰ A recent modification to the ACIP adult immunization schedule reflects effort to better target this at-risk population. Tdap is now preferentially recommended to pregnant women after 20 weeks' gestation.¹¹ On the basis of these updated indications, physicians should now seek to better identify and vaccinate adults with infant interaction and to include pregnant women and childcare workers of all ages.^{9,11}

One point of clarification recently addressed regarding Tdap administration relates to the timing of a Tdap booster relative to a

previous Td dose. In prior Tdap recommendation summaries, a period of 2 to 5 years was advised between Td and subsequent Tdap boosting.¹² More recently, however, safety data have emerged regarding shorter intervals, resulting in a modification to this recommendation. Currently, the ACIP recommends Tdap vaccination regardless of the time lapse since a previous Td booster.⁹ This recommendation comes from a review of safety data in different study populations, where Tdap-containing products were administered as quickly as 1 month after previous Td-containing immunizations. These data reported no serious adverse events associated with this shorter dosing interval and comparable local adverse reactions relative to longer durations between doses.^{13,14}

HPV immunization

Originally, the ACIP recommended routine quadrivalent human papillomavirus (HPV) vaccination (HPV4; Gardasil; Merck & Co Inc, Whitehouse Station, New Jersey) for girls aged 11 to 12 years (with a permissible age indication of 9–26 years) in an effort to decrease the burden of HPV-induced disease, most notably cervical cancer.¹⁵ This recommendation is supported by prelicensure data demonstrating vaccination efficacy of 89% or greater in patients aged 16 to 26 years relative to prevention of cervical disease and external genital lesions.¹⁵ HPV4 targets 4 specific virus types: 2 that are implicated in approximately 70% of cervical cancer (HPV types 16 and 18) and 2 that are implicated in more than 90% of genital warts (HPV types 6 and 11).^{16,17}

Cumulative data reviewing safety information after licensure suggested a disproportionate rate of reported syncope.¹⁸ Subsequent data review by the FDA resulted in a specific warning regarding syncope in female HPV-4 recipients, recommending a 15-minute period of observation after HPV-4 immunization, a recommendation reflected in the package insert.

Later, the ACIP expanded the HPV immunization recommendations to indicate that a 3-shot series of either a bivalent HPV vacci-

nation (HPV2; Cervarix; GlaxoSmithKline) (with a permissible age indication of 10–25 years) or HPV4 is appropriate for routine immunization in girls aged 11 to 12 years.¹⁹ Both vaccines contain recombinant HPV capsid proteins and are not live virus–containing vaccines. HPV2 includes HPV types 16 and 18, and data indicate similar efficacy relative to HPV4.^{20, 21} HPV2 carries the same warning statement regarding syncope as HPV4. Currently, no data are available addressing vaccine interchangeability; therefore, ACIP recommendations advise series completion using the same vaccine, if feasible.¹⁹

Recently, the ACIP provided guidance regarding HPV4 vaccination in males. Specifically, HPV4 (not HPV2) administration is now routinely recommended for all males aged 11 to 21 years. Furthermore, unvaccinated men aged 22 to 26 years who are immune compromised, who are human immunodeficiency virus (HIV) positive, or who have sex with men should also receive HPV4.²² Prospective analysis of HPV4 administration in males aged 16 to 26 years demonstrated efficacy (with respect to prevention of external male genital lesions associated with HPV types 6, 11, 16, or 18) of 90.4% in the per protocol population, with a good safety profile.²³ Clear data providing specific information regarding syncope risk in young men are not available. However, ACIP recommendations indicate a 15-minute observation period after vaccination in all patients, including males.²²

HPV4 safety and efficacy have been evaluated in women up to 45 years of age, which is of clinical relevance based on the potential for HPV protection in this large at-risk population. Comparable safety data were reported relative to younger females. Efficacy and immunogenicity data analysis is promising, suggesting a potential benefit for HPV4 immunization in women aged 24 to 45 years with limited previous HPV exposure; however, additional studies are indicated to provide supporting evidence regarding HPV disease prevention.²⁴ Also, comparative analysis of HPV4 and HPV2 regarding safety and immunogenicity was performed in women aged 18 to 45 years and indicated higher HPV types 16/18–specific antibody titers in patients who received the HPV2 series across all age subgroups.²⁵ The clinical implications of these data are unclear, however, because further study is needed to evaluate vaccine efficacy duration as it relates to antibody titer levels. Currently, no ACIP recommendation is available for HPV vaccination in this age group.¹¹

HPV has been implicated in nongenital lesions and cancers, generating considerable interest in identifying additional beneficial clinical applications for this immunization.²⁶ Notably, HPV type 6 and HPV type 11 are frequently identified in recurrent respiratory papillomatosis, a condition that is notoriously refractory to medical and surgical intervention. Otolaryngologists remain hopeful that the implementation of HPV4 vaccination will minimize the effect of this disease.^{27,28} Although case report data indicate that children with recurrent respiratory papillomatosis have benefited from HPV4 vaccination, prospective studies are indicated for further investigation, and use targeting nonanogenital HPV is considered experimental.²⁹ Similarly, HPV vaccination of physicians based on risk of potential HPV exposure is not specifically recommended.¹¹

Pneumococcal immunization

Despite no adult indication, the advent of routine pediatric pneumococcal immunization with the 7- and now 13-valent protein pneumococcal conjugate vaccine (PCV7 and PCV13; Prevnar and Prevnar-13, respectively; Wyeth Pharmaceuticals Inc, Philadelphia, Pennsylvania) has had a significant effect on invasive pneumococcal disease (IPD) rates in adults. Specifically, analysis of recent Active Bacterial Core Surveillance (ABCs) data indicates an overall decrease in IPD rate by 40% in adults aged 18 to 49 years, 18% in those aged 50 to 64 years, and 37% in adults 65 years or older relative to 1998–1999 data (pre-PCV7).³⁰ The Centers for Disease

Control and Prevention (CDC) estimates from 2009, however, reflect 44,000 cases of IPD and 5,000 deaths annually, most of which occur in adulthood, indicating a persisting call for vigilance regarding pneumococcal immunization.³¹ Furthermore, in 2006, Nowalk et al³² demonstrated that overall adult polysaccharide pneumococcal vaccination rates, when indicated, were only 45% by self-report and 55% by record review in a US cohort. Significantly, in 2006, the task force identified immunization of adults 65 years and older against pneumococcal disease as one of the most effective clinical preventive services that a health care professional can offer.³³

Recently, the ACIP published updated recommendations for administration of the 23-valent pneumococcal polysaccharide vaccine (PPSV23; Pneumovax; Merck & Co Inc). Most notably, asthma and patient smoking were added as separate, independent indications for PPSV23 in adults aged 19 to 64 years (a complete list of high-risk indications for PPSV23 administration is included in Table 2). Individuals who receive PPSV23 before 65 years of age are advised to receive a booster dose at 65 years of age or later if at least 5 years has elapsed since their first dose. One dose of PPSV23 continues to be recommended for routine immunization in adults 65 years and older, and no booster dose is indicated in this age group. Importantly, there are no situations in which ACIP advises more than 2 PPSV23 doses because of insufficient data to support this practice.³⁴

PPSV23 efficacy is supported by a Cochrane Collaboration meta-analysis indicating strong and consistent evidence of PPSV23 efficacy vs IPD.³⁵ However, when evaluating an individual previously vaccinated with PPSV23 that subsequently develops IPD secondary to a serotype included in the vaccine, the practicing immunologist must be aware of limitations surrounding PPSV23. Specifically, Shapiro et al³⁶ demonstrated that protective vaccine efficacy in this scenario in immunocompetent patients may be as low as 61%. Furthermore, Go and Ballas³⁷ demonstrated that PPSV23 responses in healthy individuals vary significantly, making postvaccination titer interpretation uniquely challenging. Generally speaking, limitations in titer interpretation across vaccinations (also regarding hepatitis B vaccination) provide supportive evidence for not routinely performing postvaccination titers in high-risk individuals in most circumstances.

In support of the updated high-risk indications, Nuorti et al³⁸ identified cigarette smoking as the strongest independent risk factor for IPD in otherwise healthy adults 18 to 64 years of age. Furthermore, recent data implicate tobacco smoking as an independent risk factor for septic shock in patients with pneumococcal pneumonia.³⁹ Although earlier, conflicting data exist regarding the degree of risk associated with asthma and IPD, Klemets et al⁴⁰ identified both low- and high-risk asthma as independent risk factors for IPD in patients aged 18 to 49 years. These 2 recently identified high-risk indicators for PPSV23 vaccination are significant because they are frequently encountered in clinical practice.

VZV immunization

Licensure of the live attenuated varicella zoster virus (VZV) vaccine (VARIVAX; Merck & Co Inc) significantly changed the guidance concerning VZV prevention in adulthood. A 2-dose immunization series, each dose administered 4 to 8 weeks apart, is recommended in susceptible adults.⁴¹ Subsequently, ACIP broadened VZV immunization recommendations to include all adults who do not meet a newly revised definition of varicella immunity. Specifically, that definition includes those individuals with documented age-appropriate vaccination, for whom there is laboratory evidence of immunity, who were born before 1980 (not including pregnant women, health care professionals, or immunocompromised individuals), or who have a history of varicella or zoster verified by a health care professional.⁴²

Subsequently, an ACIP advisory statement offering guidance on the use of a live attenuated virus vaccine to prevent herpes zoster (ZOSTAVAX; Merck & Co Inc) was published. Specifically, a single dose of zoster vaccine is indicated in adults 60 years or older without contraindication. There is no indication for booster dose administration, and there is no specific indication for routine administration in health care professionals.^{11,43} This vaccine contains the same live attenuated viral strain included in the VZV vaccine (Oka strain) but with a minimum potency of at least 14 times that of VARIVAX.⁴³ Interestingly, unlike most other live attenuated viral vaccines (including varicella and MMR) when a 3- to 11-month wait time is indicated, zoster vaccine can be given at any time relative to administration of blood products.^{43,44}

Recent VZV immunization recommendations were incited by an effort to prevent herpes zoster and its sequelae in adulthood. Separate data from Taiwan and the United States indicate increased disease incidence and complication rates with advancing age, with a notable increase in disease rate after 40 to 50 years of age. The estimated lifetime risk of developing VZV is approximately 30%.^{45,46} Herpes zoster has been implicated in severe adverse neurologic outcomes, including fatal encephalitis, and overall hospitalization rates of approximately 3%.^{45,47,48} More commonly, however, Yawn et al⁴⁷ demonstrated that approximately 10% to 18% of patients experience postherpetic neuralgia, which can be severely debilitating. Furthermore, data indicate that approximately 20% of patients have ocular involvement, with risk of lasting sequelae, including blindness.⁴⁹

Currently, no evidence indicates that natural zoster infection is protective against recurrence, and individuals with a history of zoster infection can be immunized with the zoster vaccine.⁴³ Mills et al⁵⁰ provided supporting evidence for vaccination in this scenario through prospective study of a cohort of individuals 50 years or older with a history of herpes zoster who were immunized with the zoster vaccine. A postvaccination boost in antibody titers and absence of serious adverse reactions in this population provide evidence of both vaccine immunogenicity and clinical tolerability. Although an uncommon clinical scenario, zoster vaccination is not currently recommended for individuals who have received varicella vaccine.⁴³ Currently, no published data are available regarding VZV immunization in this notably small patient subset.

As is the case with all live attenuated immunizations, VZV vaccine is generally contraindicated in immunocompromised persons. In the setting of anticipated immunosuppression, vaccination 14 days before immunocompromise is advised.⁴³ Pre-immunocompromise immunization with the vaccine is specifically important because immunocompromise is associated with a significant increase in zoster infection severity and postherpetic disease burden.⁵¹

Oxman et al⁵² reported VZV vaccine efficacy data that demonstrated a reduction of VZV incidence of 51% in vaccinated individuals 60 years or older, resulting in a significant decrease in overall disease burden. Data are promising with regard to the decreased risk of postherpetic neuralgia; however, continued investigation is indicated to provide further direct supportive evidence.^{52,53}

One open issue regarding zoster immunization involves contemporaneous vaccination with PPSV23. MacIntyre et al⁵⁴ provided evidence indicating that zoster antibody response to simultaneous PPSV23 and zoster vaccine administration was significantly lower than levels when the zoster vaccine was administered 4 weeks after PPSV23 in patients 60 years or older. This finding resulted in revision of the ZOSTAVAX package insert, advising consideration of zoster vaccine administration 4 weeks separate from administration of PPSV23. Because there is currently no evidence to indicate that specific zoster antibody levels correlate with degree of zoster protection, the clinical significance of these data remains unclear. As a result, the ACIP has not modified their recommendation that

both zoster vaccine and PPSV23 can be administered simultaneously.⁵⁵ The current recommendation is supported by an observational study by Tseng et al⁵⁶ that demonstrated no difference in risk of zoster infection in 2 patient cohorts 60 years or older in which patients received either zoster vaccine and PPSV23 separated by 30 days to 1 year or both vaccines contemporaneously.

Recently, the FDA approved an indication for VZV vaccine administration to individuals 50 to 59 years of age. However, current ACIP recommendations do not reflect this change.^{11,43}

Meningococcal immunization

With the development and licensure of 2 conjugated tetravalent meningococcal vaccinations (MVC4, with coverage of serogroups A, C, Y, and W-135; Menactra [Sanofi Pasteur] and Menveo [Novartis, Basel, Switzerland]), routine vaccination, as advised per the ACIP's pediatric vaccine schedule, has resulted in a notable decrease in rates of invasive meningococcal disease. However, postlicensure data suggest that adolescents may not be protected for more than 5 years after vaccination.⁵⁷ As a result, MVC4 is routinely indicated in military recruits and first-year college students up to 21 years of age who are living in residence halls if they have not received a dose on or after their 16th birthday.¹¹ Interestingly, some states mandate meningococcal vaccination in all college students, which may include postgraduate students. Such a mandate would represent an exception to the current recommendations in many instances because it would include a population of individuals older than 21 years.

Vaccination of high-risk patients

General overview

In addition to the intricacies associated with routine adult immunization, a strategy for vaccination of high-risk patients involves additional complexities. In particular, vaccine-specific high-risk identifiers differ, and immunization response rates in specific high-risk populations also vary. However, as with routine adult immunization, a simplified approach to vaccination of high-risk patients can facilitate a more feasible strategy for optimized vaccine rates. Table 2 was constructed referencing ACIP recommendations for high-risk vaccination, with footnotes highlighting the vaccine-specific high-risk identifiers.¹¹ The objective of the table is not to recreate the well-constructed ACIP chart for immunization recommendations but rather to serve as a simplified source to assist in high-risk patient identification. The goal is to improve vaccination rates by providing targeted patient counseling and to ensure appropriate vaccine responsiveness in specific populations.

In addition to the high-risk identifiers included in Table 2, this section provides specific guidance targeting circumstances that will alter vaccine-specific recommendations in this patient subset. For example, data specific to asplenic patients serve as (1) detailed information referencing a specific high-risk population where vaccination is highly advantageous but where rates are currently suboptimal and (2) a high-risk identifier that provides a model for vaccine implementation, as it applies to individuals with other high-risk conditions. Specific information regarding hepatitis B responsiveness has implications for consideration of repeat series vaccination and high dosing recommendations.

Asplenia: Immunization guidance with implications for other high-risk patients

The term *asplenia* applies to individuals across a broad range of medical specialties without effective splenic function. This term includes both anatomical (eg, splenectomy after trauma or malignant tumor) and functional (as in sickle cell anemia) asplenia. Such individuals are at increased susceptibility for invasive infections, including those due to encapsulated bacteria. Although *Streptococ-*

cus pneumoniae accounts for 80% to 90% of sepsis in asplenic patients, postsplenectomy patients are also at risk for other encapsulated pathogens, including *Neisseria meningitidis* and *Haemophilus influenzae* type b (Hib).⁵⁸ As a result, the ACIP recommends immunization to these pathogens, in conjunction with routine adult immunizations in asplenic patients (Tables 1 and 2).⁴⁴

Vaccination rates in asplenic patients have improved as a result of implemented targeted vaccination protocols. However, data from a population of nearly 600 splenectomy patients in Spain demonstrated vaccination rates for pneumococcus, Hib, and meningococcus of 63%, 63%, and 61%, respectively, despite such a protocol.⁵⁹

Asplenic adult patients, as well as other high-risk patients identified in Table 2, aged 18 to 64 years should receive 2 doses of PPSV23 vaccine 5 years apart (again, only 1 dose is indicated if administered at 65 years or older).¹¹ Analysis of the ABCs data indicates a decrease in IPD rates in adults as a result of pediatric use of the PCV. Evidence indicating a corresponding increase in non-PCV7 serotypes (including serotype 19A), however, lends support to the recent recommendation for a transition from a 7- to 13-valent pediatric PCV that includes additional serotypes, including 19A.³⁰ Although there is no adult indication for the PCV, older children and adolescents (aged 6–18 years) who have not previously received PCV13 may receive 1 dose of the vaccination.⁶⁰ This scenario is clinically relevant because, although PPSV23 contains all of the serotypes included in PCV7, there is 1 serotype (6A) that is unique to PCV13 and not included in PPSV23.

Meningococcal vaccination is indicated in asplenic patients and additional high-risk patients identified in Table 2.¹¹ Specifically, both conjugated tetravalent meningococcal vaccinations (Menactra and Menveo) are indicated for high-risk individuals aged 2 to 55 years and administered initially as a 2-dose series with doses separated by at least 2 months. In at risk patients 56 years or older, 1 dose of the meningococcal polysaccharide vaccine MPSV4 (Menomune; Sanofi Pasteur) is preferred, which covers the same serogroups as the conjugate vaccine.¹¹ On the basis of the uncertainty regarding the duration of protective meningococcal titers, all adults who remain high risk should receive repeated meningococcal vaccination at a 5-year interval, with either MCV4 (age 2–55 years) or MPSV4 (age =56 years).^{44,57}

Current data supporting the efficacy of Hib vaccine in asplenic adults are limited. Evidence indicates long-term persistence of immunity when evaluating older children vaccinated in infancy.⁶¹ Data from a small population of asplenic Eastern European adults who received the Hib vaccine in conjunction with pneumococcal vaccination demonstrated a positive response, but results are preliminary.⁶² Overall, ACIP guidelines note that a single dose of the Hib vaccine in previously unimmunized adults should be considered in individuals with asplenia, HIV, or leukemia.¹¹

Pneumococcal, meningococcal, and Hib vaccines should be administered at least 2 weeks before elective splenectomy. If not given before surgery, these immunizations are to be administered after the patient has stabilized in the postoperative period, with data indicating better functional pneumococcal antibody responses at 14 days after splenectomy compared with vaccination at 1 or 7 days after the procedure.^{44,63}

Hepatitis B immunization and implications of vaccine responsiveness

Clinical implications surrounding hepatitis B responsiveness merit specific discussion because dosing varies, depending on the identified risk factors. In addition, allergists-immunologists may encounter inquiries regarding the interpretation of postvaccination serologic test results and subsequent management recommendations. Although vaccine nonresponsiveness is uncommon in healthy young adults, protection is compromised by suboptimal series completion rates and specific clinical variables that impair

immune response, including advancing age.⁶⁴ It is therefore imperative that practicing allergists-immunologists take an active role to ensure vaccination series completion and monitor for situations where serologic testing, revaccination, and/or higher-dose immunization are indicated.

Hepatitis B vaccines currently available in the United States contain 5 to 40 $\mu\text{g/mL}$ of hepatitis B protein. They are routinely administered intramuscularly in a 3-shot series. Specific indications for immunization are included in Table 2. Recommendation for postvaccination serologic testing 1 to 2 months after the final dose of the primary series to ensure responsiveness is only indicated in the following patient populations: health care and public safety workers, long-term hemodialysis patients, sex partners of hepatitis B surface antigen–positive individuals, HIV-infected patients, and other immunocompromised patients (including patients undergoing organ transplantation and/or chemotherapy). Individuals with a hepatitis B surface antibody titer of 10 mIU/mL or higher are considered protected.⁶⁵

Among those for whom vaccination is indicated based on risk factors, hepatitis B series completion in the United States is approximately 55% to 71%, with lowest adult rates of series completion noted in the 18- to 29-year-old age range.⁴ Acceptable hepatitis B protection in healthy young adults is contingent on completion of the conventional 3-shot series because single-dose vaccine responsiveness in healthy adults 40 years of younger is approximately 43% to 58%.^{66,67} In contrast, data indicate protection rates greater than 90% to 95% in healthy adults 40 years or younger when measured between 1 and 3 months after 3-shot series completion.^{66,68} Decreased and potentially undetectable hepatitis B surface antibody titers are noted in the period after series completion, regardless of the age at which immunization series is initiated.^{69,70} In a cohort of infants who completed the routine 3-shot series, 90% demonstrated protective titers 6 months after completion, whereas only 41% had protective titers at 60 months.⁶⁹ However, long-term protection, when considering both patients with persisting protective titers and those who demonstrate a protective anamnestic booster response, remains above 80% when evaluated up to 22 years after completion of the primary series.⁷⁰

Immunocompromise (including HIV) and end-stage renal disease requiring hemodialysis represent chronic conditions that have been specifically implicated in suboptimal vaccination response.^{71,72} Importantly, vaccine administration before or early in the clinical course in both patient populations results in greater rates of hepatitis B seroprotection.^{71,73} Higher hepatitis B vaccine dosing (40 $\mu\text{g/mL}$ per dose) has been implicated in improved seroprotection in these high-risk patient subsets.^{74,75}

Current vaccine recommendations were implemented in an effort to target these limitations regarding hepatitis B seroprotection rates. Evidence from repeating the 3-dose hepatitis series once in healthy adult nonresponders with an indication for routine hepatitis B immunization reflects response rates after readministration of the 3-shot series varying from 45% to 100%.^{76,77} Current ACIP guidance advises modifying hepatitis B immunization doses and schedules in an effort to enhance responsiveness in immunodeficient and/or hemodialysis-dependent patients with a 3- or 4-shot, high-dose series (40 $\mu\text{g/mL}$ per dose), as reflected in Table 2, to augment responsiveness.¹¹ Optimal reimmunization schedules for high-risk patients who do not respond to higher-dose vaccination are not clearly defined.

Recently, a subset of patients not uncommonly encountered in the office of a practicing allergist, namely, diabetic patients aged 19 to 59 years, was identified as a high-risk patient population where hepatitis B vaccine is indicated. This recommendation was initiated based on a series of hepatitis B virus infection outbreaks involving adults receiving assisted blood glucose monitoring and concern for potential comorbid liver disease in diabetic patients portending a

poorer prognosis. Vaccination of older diabetic patients (aged ≥ 60 years) is recommended at the discretion of the physician based on risk stratification, with consideration of impaired vaccine responsiveness based on age.⁷⁸

Practical references

One obvious challenge regarding the complex topic of immunization is the difficulty in remaining current in a rapidly evolving field. The ACIP publishes updated general immunization recommendations and schedules annually, as well as timely vaccine-specific recommendation updates, in the CDC's *Morbidity and Mortality Weekly Report* (<http://www.cdc.gov/mmwr>).

The Military Vaccine Agency (<http://www.vaccines.mil/>) is the US Department of Defense vaccination program dedicated to providing educational support to health care professionals caring for military service members and their families. This site has practical value for all health care professionals, military and civilian alike. The homepage serves as a direct link to the following:

- ACIP updates on general immunization recommendations⁴⁴
- Annually updated ACIP recommended immunization schedules¹¹
- The CDC's most current traveler's health information (including a link to the CDC Yellow Book—a trusted reference for destination-specific traveler's health information for medical professionals)
- The CDC Pink Book—a comprehensive source of vaccine-preventable disease information for health care professionals
- Vaccine- and disease-specific reference materials, including updated vaccine package inserts, vaccine-specific ACIP guidelines, and targeted vaccine news updates

The CDC's most updated annual recommended adult immunization schedule contains a practical table referencing immunization-specific contraindications and precautions.¹¹ To ensure currency, health care professionals can also use the Immunization Action Coalition's webpage, which provides all ACIP vaccine recommendation updates (including updates targeting specific patient populations, such as pregnant patients, and annually modified vaccine recommendations, including influenza) listed in order of publication (www.immunize.org/acip).

Adverse vaccine events can pose unique challenges to practicing physicians. The Clinical Immunization Safety Network (<http://www.cdc.gov/vaccinesafety/Activities/cisa.html>) provides concerned health care professionals with a link to experts in vaccinology and vaccine safety across 6 academic medical centers nationwide. These experts review complex vaccine safety cases to assist in developing general assessments and plans.

Conclusion

Current evidence reflecting suboptimal immunization rates for vaccine-preventable disease confirms the existence of real and perceived barriers to adult immunization. In an effort to overcome these barriers, practicing allergists-immunologists must accept an active role in remaining updated on the practical aspects of immunization and relaying this needed information in an effective manner to patients and families. Even though the field of vaccine medicine is constantly and quickly evolving, practical resources are available to maintain currency.

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