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A Review of Current Vaccine Recommendations, Schedules for Children, Adults

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At this unprecedented time of practicing medicine during the coronavirus pandemic, the focus on vaccines has never been more important.

Healthcare professionals of all backgrounds must remain up to date with the knowledge base regarding available vaccines and we must stay confident in our communications. We need to reach the ears, hearts and beliefs of our patient population – we are truly the ambassadors for the broad delivery of vaccines. We have the ability to protect our patients and ourselves from diseases that used to regularly sicken and even kill us!

Dr. Jennie Johnson and I and our colleagues working in the field of Infectious Diseases are delighted to create this special themed issue of the *Rhode Island Medical Journal* (RIMJ) to review the **latest vaccine updates** that can help all practitioners have a continuous dialogue about vaccine-preventable illness with our patients at every visit.

We review the **influenza vaccine** with tips on how to engage the patient. Practitioners get more push back on this vaccine than all of the others. It's of great importance that both primary care practitioners and specialists advocate for the flu vaccine. Cardiologists, for example, can present the standpoint that influenza is linked to an increased rate of myocardial infarction.

Adjustment and fine-tuning of the use of **pneumococcal pneumonia vaccines** was published in late 2019 due to a remarkable observation: vaccination of children with conjugate vaccines against the pneumococcus has dramatically reduced disease in older individuals.

All adults age 19 and older who have never had a dose of **Tdap** should get one as soon as possible, regardless of the interval since the last tetanus or diphtheria toxoid-containing vaccine. Pertussis, like influenza and pneumococcal pneumonia, may confuse the clinical evaluation of persons with coronavirus and can cause protracted respiratory symptoms that are now preventable. As students return to college campuses, two types of protection against **meningococcal meningitis** – also spread by respiratory droplets – is mandatory.

Prevention of shingles with the **recombinant varicella zoster vaccine** is now safer, more highly effective and longer lasting than the former live attenuated vaccine.

Broad recommendations for **hepatitis A and B vaccines** for US adults can help avoid infectious risks both during travel abroad as well as from increased local transmission.

Vaccine hesitancy clouds the mission of protection of the entire population. Educating, supporting and hopefully vaccinating individuals who may harbor selfish or unfounded fears may protect our vulnerable immunosuppressed individuals. A powerful opinion piece included here outlines the issues, including the increased number of US **measles** cases.

As guest editors we are perpetually optimistic that the world will heal and will desire to travel again – and that people take their flu shot and coronavirus shot, too! The latest Advisory Committee on Immunization Practices (ACIP) guidelines updated the recommendation to broaden use of the **Japanese encephalitis vaccine** for many travelers to Asia. We reviewed this vaccine as well as the **rabies vaccine.** In addition**,** the **Yellow Fever** vaccine shortage persists nationwide, yet remains available at our designated site at the Brown Medicine travel clinic.

The coronavirus pandemic, due to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that originated in Wuhan china in late 2019 and has spread worldwide as of March 2020, has left us more isolated than ever.

We only wish we had a vaccine for this virus! This pandemic is the most significant current-day scourge the world is facing. We are excited that our Infectious Disease Division at Brown will be participating in research to develop safe and efficacious COVID vaccines.

The potentially strongly enthusiastic uptake of a coronavirus vaccine may pave the way for more individuals to adopt the other vaccines that have helped stem the past epidemics of polio, measles, mumps and many other processes, to keep those illnesses from resurfacing. We have to engage conversations empowered with up-to-date knowledge. It may help to use accounts of past outbreaks to illustrate how vaccines help us stamp out diseases before we need to deal with disease repercussions.

As practitioners we must convey a unified message. Vaccines do not cause autism. Vaccines help us go to school, help us travel to learn about other places and cultures and appreciate each other and help us see our grandparents. Vaccines help keep us together.

We can't emphasize this message strongly enough – it will take a shot in the arm!

Guest Editors

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Talking to Patients about the Influenza Vaccine

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ABSTRACT

Influenza is a significant cause of hospitalization and death in late fall and early spring, especially in our most vulnerable populations. Despite high mortality and morbidity of influenza infection, patients are still hesitant about getting the flu vaccine each year. This article offers advice on educating our patients to address misconceptions and help them embrace this important seasonal vaccination.

KEYWORDS: influenza, vaccine hesitancy, flu, cardiovascular risk, COVID

INTRODUCTION

Influenza is a common seasonal and often severe respiratory illness that affects humans and animals. It was first isolated in 1933 and has caused multiple pandemics since its discovery, with the most recent occurring in 2009 due to Influenza A/H1N1. Influenza is spread from person to person primarily through inhalation of infected droplets when a person coughs, sneezes, or speaks.[1] Individuals with influenza can shed the virus in the absence of symptoms. Once symptomatic, they are infectious up to 7 days after onset.[2] The most common symptoms on presentation include fever, cough, body aches and headache, yet most people recover without persistent sequelae.[3] However, through late fall and early spring it is a significant cause of hospitalization and even death, especially in our most vulnerable populations which include elderly, chronically ill individuals, pregnant women, and young children.[4,5] Annually, tens of millions worldwide are infected with influenza. According to the Centers for Disease Control and Prevention (CDC), in the 2018–2019 influenza season, ~35.5 million Americans were infected with influenza, which resulted in ~34,000 deaths.[6]

Despite high morbidity and mortality from influenza, patients are still hesitant about getting the influenza vaccine each year.[7] Most people recognize that vaccination is one of the most important public health interventions in the 21st century. Elimination of smallpox worldwide and elimination of polio in most of the world are two major accomplishments attributed to vaccinations.[8] However, when it comes to influenza vaccine, it is more challenging to convince patients to get their influenza vaccine. Notably, only 49% of the US population received the influenza vaccine in the 2018–2019 influenza season according to the CDC.[6] Here is a summary of key points to use when speaking to your patients about the influenza vaccine.

1: Offer the influenza vaccine

The first step to talking to patients about vaccination is to actively offer the influenza vaccine in a positive manner. Provider recommendation is a strong factor in convincing patients to be vaccinated.[9,10] In general, patients have trust in the person who is providing medical care for them. This is especially true if the provider has been caring for them for an extended length of time. As medical providers, we have a unique role in educating our patients about different diseases. When we take advantage of the opportunity to educate our patients about the rationale behind influenza vaccination and address misconceptions, they are less likely to internalize false information from family, friends, co-workers, and social media. Considering the COVID-19 pandemic there is heightened awareness on prevention of other respiratory infections. After offering the influenza vaccination, we should go into more detail on why it is so important.

2: Explain the importance of Influenza vaccination

Vaccination against influenza reduces the risk of significant illness that requires evaluation by a medical professional or hospitalization by 40–60%.[11] It decreases influenza-related hospitalization, hospital death, and ICU admission associated with influenza.[3] The Benowitz, et al 2010 study showed the vaccination of pregnant women was over 90% preventive of hospitalization of their infants due to influenza in the first 6 months of life. Unfortunately, the efficacy of the influenza vaccine is about 40%.[4] While it may be true that it will not prevent all vaccinated persons from infection, it may ameliorate the clinical presentation to a less severe illness. Lastly, studies show that illness due to the flu is associated with secondary increases in heart attacks and stroke, which provides patients, especially persons with heart disease, a reason for influenza vaccination.[12]

3: Know your audience

As medical professionals, we can appreciate the benefits of influenza vaccinations and have likely taken care of patients

who have had complications from influenza. However, many patients have either never had it, was infected and do not remember having influenza, or had a mild case and fully recovered. Consequently, focusing on death rates from influenza will likely not mean much to your patient. Therefore, when speaking with patients, focus on explaining that influenza vaccination is our primary prevention strategy to combat severe illness from this infection and to prevent them from spreading influenza to more vulnerable persons. Reiterate that if your patient were to be infected with an influenza strain that was not included in the vaccine, it may ameliorate the disease so that he or she will be less sick from this infection than someone who did not get vaccinated. Stress that it may keep your patient out of the hospital if he or she does catch the flu. It may even prevent having a heart attack or stroke. At this point, your patient may bring up some questions/concerns about the influenza vaccines.

MOST COMMON QUESTIONS ABOUT INFLUENZA VACCINE

Why do we have to get the flu shot every year?

Influenza is encapsulated by an envelope that contains host-derived lipid membrane and viral proteins including hemagglutinin (HA), neuraminidase (NA), matrix 1 (M1), and matrix 2 (M2). Infection of host cells occur when HA binds to the host cell, which triggers endocytosis of the virus. Once inside, M1 and M2 are activated resulting in the release of viral RNA into the cytoplasm and through a complex series of steps, transportation in to the host nucleus. Viral RNA-dependent RNA polymerase transcribes and replicates influenza.[13] However, this polymerase activity is known to be error-prone. Therefore, inaccuracies in replication results in production of slightly different influenza strains, which explains the propensity for influenza to have antigenic drift. Antigenic drift occurs when an accumulation of mutations in the viral genome results in small changes. However, over time, these errors produce antigenically different influenza strains.[14] Since the influenza vaccines target antigens on the envelope, the influenza vaccine needs to change each year with the hopes of including protection against the most predominant strains that year.

The significant changes needed in the influenza vaccines from year to year are evident by **Figure 1**, which shows the viruses used for the egg-based quadrivalent influenza vaccine by year. Only 1 influenza strain (B/Phuket/3073/2013 (B/Yamagata lineage)-like virus used in the vaccine formulation remains the same between the 2019–2020 season and the 2020–2021 season.

The following analogy simplifies the above answer for patients. Think of the envelope of the influenza virus as a coat. The buttons on the coat represent antigens on the envelope. When the vaccine gets into the system, it is looking to target the buttons on the coat. However, the virus learns this and adapts by either changing the buttons on its coat or changing its coat completely. This is happening all of the time. Therefore, the initial vaccine given becomes ineffective because the virus has changed. This is why influenza vaccine changes yearly. It's trying to keep up with the fashion choices of the influenza virus.

I have an egg allergy. Can I get the flu shot?

Inactivated influenza vaccine (IIV) and live attenuated influenza vaccines (LAIV) are the two types of vaccines available in the US against influenza. Formulations of other influenza vaccines are found in the table below (**Table 1**). All available vaccines are egg-based with the exception of recombinant Influenza vaccine (RIV4), which is a good option for patients with severe egg allergies.[1] Contraindications for influenza vaccine include history of severe allergic reaction to any component of the influenza vaccine.

FluMist is an example of the live attenuated vaccine that is administered via nasal spray. It can be given to people ages 2–49 years old. It is a safe alternative for individuals with aversion to needles. However, the following are contraindications to the live-attenuated influenza vaccine:

- Children and adolescents on aspirin or salicylate containing therapy
- Children aged 2-4 years old with asthma or wheezing within the last 12 months prior to vaccination
- Any immunocompromised persons
- Close contacts and caregivers of severely immunocompromised persons
- Pregnancy
- Administration of influenza antiviral medications in the last 48 hours[1,15]

Figure 1. Egg-Based quadrivalent influenza viruses used for vaccine by season

2019–2020 season	2020–2021 season
A/Brisbane/02/2018 (H1N1)pdm09-like virus	A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09-like virus
A/Kansas/14/2017 (H3N2)-like virus	A/Hong Kong/2671/2019 (H3N2)-like virus;
B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage);	B/Washington/02/2019 (B/Victoria lineage)-like virus
B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage)	B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

Table 1. Influenza vaccines – United States, 2019–2020 influenza season*

Trade name (Manufacturer)	Presentation	Age indication	HA (IIVs and RIV4) or virus count (LAIV4) for each vaccine virus (per dose)	Route	Mercury (from thimerosal) (μg/0.5mL)
IIV4—Standard Dose—Egg based†					
Afluria Quadrivalent (Seqirus)	0.25-mL PFS§	6 through 35 mos	7.5 μg/0.25 mL§	IM¶	—
	0.5-mL PFS§	≥3 yrs	15 μg/0.5 mL§		—
	5.0-mL MDV§	≥6 mos (needle/syringe) 18 through 64 yrs (jet injector)			24.5
Fluarix Quadrivalent (GlaxoSmithKline)	0.5-mL PFS	≥6 mos	15 μg/0.5 mL	IM¶	—
FluLaval Quadrivalent (GlaxoSmithKline)	0.5-mL PFS	≥6 mos	15 μg/0.5 mL	IM¶	—
	5.0-mL MDV	≥6 mos			<25
Fluzone Quadrivalent (Sanofi Pasteur)	0.25-mL PFS**	6 through 35 mos	7.5 μg/0.25 mL**	IM¶	—
	0.5-mL PFS**	≥6 mos	15 μg/0.5 mL**		—
	0.5-mL SDV**	≥6 mos			—
	5.0-mL MDV**	≥6 mos			25
IIV4—Standard Dose—Cell culture based (ccIIV4)					
Flucelvax Quadrivalent (Seqirus)	0.5-mL PFS	≥4 yrs	15 μg/0.5 mL	IM¶	—
	5.0-mL MDV	≥4 yrs			25
IIV3—High Dose—Egg based† (HD-IIV3)					
Fluzone High-Dose (Sanofi Pasteur)	0.5-mL PFS	≥65 yrs	60 μg/0.5 mL	IM¶	—
IIV3—Standard Dose—Egg based† with MF59 adjuvant (aIIV3)					
Fluad (Seqirus)	0.5-mL PFS	≥65 yrs	15 μg/0.5 mL	IM¶	—
RIV4—Recombinant HA					
Flublok Quadrivalent (Sanofi Pasteur)	0.5-mL PFS	≥18 yrs	45 μg/0.5 mL	IM¶	—
LAIV4—Egg based†					
FluMist Quadrivalent (AstraZeneca)	0.2-mL prefilled single-use intranasal sprayer	2 through 49 yrs	$10^{6.5–7.5}$ fluorescent focus units/0.2 mL	NAS	—

Abbreviations: ACIP = Advisory Committee on Immunization Practices; FDA = Food and Drug Administration; HA = hemagglutinin; IIV3 = inactivated influenza vaccine, trivalent; IIV4 = inactivated influenza vaccine, quadrivalent, IM = intramuscular; LAIV4 = live attenuated influenza vaccine, quadrivalent; MDV = multidose vial; NAS = intranasal; PFS = prefilled syringe; RIV4 = recombinant influenza vaccine, quadrivalent; SDV = single-dose vial.

* Vaccination providers should consult FDA-approved prescribing information for 2019–20 influenza vaccines for the most complete and updated information, including (but not limited to) indications, contraindications, warnings, and precautions. Package inserts for U.S.-licensed vaccines are available at https://www.fda.gov/vaccines-blood-biologics/approved-products/vaccines-licensed-use-united-states. Availability of specific products and presentations might change and differ from what is described in this table and in the text of this report.

† Persons with a history of egg allergy may receive any licensed, recommended influenza vaccine that is otherwise appropriate for their age and health status. Those who report having had reactions to egg involving symptoms other than urticaria (e.g., angioedema or swelling, respiratory distress, lightheadedness, or recurrent emesis) or who required epinephrine or another emergency medical intervention should be vaccinated in an inpatient or outpatient medical setting (including, but not necessarily limited to, hospitals, clinics, health departments, and physician offices). Vaccine administration should be supervised by a health care provider who is able to recognize and manage severe allergic reactions.

§ The dose volume for Afluria Quadrivalent is 0.25 mL for children aged 6 through 35 months and 0.5 mL for persons aged ≥3 years.

¶ Intramuscularly-administered influenza vaccines should be given by needle and syringe only, with the exception of the MDV presentation of Afluria Quadrivalent, which may alternatively be given by the PharmaJet Stratis jet injector for persons aged 18 through 64 years only. For adults and older children, the recommended site for IM influenza vaccination is the deltoid muscle. The preferred site for infants and young children is the anterolateral aspect of the thigh. Additional guidance regarding site selection and needle length for intramuscular administration is available in the ACIP General Best Practice Guidelines for Immunization (https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf).

** Fluzone Quadrivalent may be given to children aged 6 through 35 months as either 0.25 mL per dose or 0.5 mL per dose. No preference is expressed for one or the other dose volume for this age group. Persons aged ≥3 years should receive the 0.5-mL dose volume.

Who should get the flu shot?

Generally, all persons 6 months old and older should receive the influenza vaccine by the end of October. Vaccines for the 2020–2021 are available for pre-order by clinics and health-care facilities but they will not be available to the public until October 2020. Children between ages 6 months to 8 years old who are receiving the influenza vaccination for the first time require 2 doses separated by 4 weeks. The first dose should be given in children who require 2 doses as soon as possible so that the 2nd vaccination can be given by the end of October.[15]

The following people have the highest risk of medical complications from severe influenza infection according to the ACIP at CDC:

- All children aged 6 through 59 months;
- All persons aged ≥50 years;
- Adults and children who have chronic pulmonary (including asthma), cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus);
- Persons who are immunocompromised due to any cause (including but not limited to immunosuppression caused by medications or HIV infection);
- Women who are or will be pregnant during the influenza season;

- Children and adolescents (aged 6 months through 18 years) who are receiving aspirin or salicylate-containing medications and who might be at risk for experiencing Reye's syndrome after influenza virus infection;
- Residents of nursing homes and other long-term care facilities;
- American Indians/Alaska Natives; and
- Persons who are extremely obese (body mass index ≥40 for adults)

I am healthy and I never get the flu. Why should I be vaccinated?

In healthy individuals, influenza may present as a severe cold and that person fully recovers. In fact, that person may never present to the healthcare system for testing.[2] However, if they live with a vulnerable person such as pregnant women or children < 6 months old, they can unknowingly pass the virus to that vulnerable person or surrounding community which can result in severe disease in the compromised person and infection in persons within their community.[14] Explaining this to patients is important to get them to understand the risk they can place on other household members.

The flu shot gives you the flu

It is important to remind patients that they are not being injected with the influenza virus when they receive the influenza vaccine. Therefore, it is not possible for them to actually contract influenza from the influenza vaccine. Typically, symptoms include redness and soreness at the injection site. However, some people do feel ill after vaccinations and this can be attributed to the following reasons:

Exposure to another respiratory virus. There are many viruses that cause influenza-like symptoms, which include rhinovirus, adenovirus, coronavirus. The influenza vaccine does not provide protection against these so if someone was exposed to them, then they will fall ill.

Low-grade fever, headache, and muscle aches are less common adverse effects of the influenza vaccine but it does occur. These symptoms represent a healthy immune response to the vaccine. Usually, these symptoms resolve in 1–2 days post-vaccination. However, they are uncomfortable and can be mistaken for a case of the mild flu.

It takes about 2 weeks for the body to mount an immune response that is protective against influenza. However, if a patient is exposed to the virus a few days before vaccination or in the 2-week period after vaccination, they can come down with influenza because their body did not have protection against it.

Lastly, vaccine manufactures predict the 3–4 most predominant influenza strains and create a vaccine against them. However, patients can get influenza strains that are not covered by the influenza vaccination and subsequently become sick from influenza.

Taking the time to review above scenarios will help alleviate patient concerns about getting ill from the influenza vaccine.

CONCLUSION

Influenza infection continues to cause high morbidity and mortality among Americans yearly, affecting the most vulnerable people such as young children.[1,14] In an environment where there is more distrust about vaccines than in the past, talking to patients about influenza vaccination is challenging to providers. However, studies have shown that patients listen to medical providers about vaccines.[8] Additionally, changing in-office practices regarding vaccination including sending patient reminders about upcoming flu shot, posting facts about influenza in the waiting/exam room, and creating standing orders or order sets in the electronic medical record can make having this important conversation with patients much easier.[9]

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Recent Updates to the Advisory Committee On Immunization Practices Recommendations for Pneumococcal and Herpes Zoster Vaccination

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ABSTRACT

Pneumococcal and herpes zoster – shingles – vaccination prevent a great deal of morbidity, particularly in elderly and immunocompromised hosts. Vaccination of children with conjugate pneumococcal vaccine in recent years has greatly reduced illness in older individuals as well. This article will review the historical and current recommendations for pneumococcal and herpes zoster vaccination and the rationale for changes at the level of the CDC's Advisory Committee on Immunization Practices.

KEYWORDS: vaccination, immunization, conjugate pneumococcal vaccine, herpes zoster, shingles

PNEUMOCOCCAL VACCINATION

Background

S. pneumoniae is the most commonly identified pathogen in community-acquired pneumonia (CAP) worldwide and can cause serious illness, particularly among young children, the elderly, or those with immunocompromising conditions. Severe infection may lead to invasive pneumococcal disease (IPD), including pneumococcal bacteremia or meningitis, which can result in significant neurological sequelae and death. The financial burden of IPD to the US healthcare system is substantial and is estimated to increase by $2.5 billion annually in the coming decades with an aging population.[1]

Historical ACIP Recommendations for Pneumococcal Vaccination

There are currently two licensed vaccines approved for the prevention of pneumococcal disease in the US: the 23-valent pneumococcal polysaccharide vaccine (PPSV23, [Pneumovax 23, Merck and Co., Inc]), containing antigens from 23 common serotypes, and the 13-valent pneumococcal conjugate vaccine (PCV13 [Prevnar 13, Pfizer, Inc.]), containing antigens from 13 common serotypes. There is considerable overlap among the antigens contained within each vaccine; 12 of the 13 antigens in PCV13 are common to PPSV23 apart from serotype 6A.

Recommendations for pneumococcal vaccination have evolved over time based on shifts in the epidemiology of IPD and as new products have been introduced into market. PPSV23 was first licensed in 1983 and was subsequently introduced into the routine schedule for all adults ≥65 years and for those ≥2 years with certain underlying medical conditions.[2] In 2000, the 7-valent pneumococcal conjugate vaccine (PCV7) was introduced into the routine pediatric schedule for all children <5 years, and in 2010, the approval of PCV13 led to replacement of PCV7 with PCV13 in the pediatric schedule.[3] In 2012, indications for PCV13 were broadened to all individuals ≥19 years with immunocompromising conditions, administered in series with PPSV23 eight weeks later.[4] In 2014, results from the randomized placebo-controlled Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) demonstrated that 20–25% of IPD and 10% of CAP cases in adults ≥65 years were caused by PCV13 serotypes and were potentially preventable.[5] This prompted the 2014 ACIP recommendation for vaccination with both PCV13 followed by PPSV23 ≥ one year later in all immunocompetent adults at age 65.[6,7]

Updated ACIP Recommendations for Pneumococcal Vaccination

Historical vaccination efforts in the pediatric patient population have been essential to decreasing overall pneumococcal disease burden, morbidity, and mortality both directly and indirectly through reduction in carriage and transmission to adults.[8] In 2019, ACIP reviewed the evidence over the preceding three years to determine if there was a continued need for PCV13 vaccination in elderly immunocompetent adults in series with PPSV23 versus PPSV23 alone. A systematic review was conducted including twenty studies published from 2014–2018 to evaluate data on the safety, efficacy, and cost-effectiveness of pneumococcal vaccination in this patient population. Results demonstrated that from 2000-2014, widespread uptake of pediatric pneumococcal vaccination in the US led to a ninefold decrease in the incidence of PCV13-type IPD in adults ≥65 through reduced carriage and transmission. A similar effect was seen for those at increased risk due to age or chronic medical conditions. From 2014–2018, the incidence of PCV13-type IPD in adults ≥65 has remained stable (5 cases per 100,000), with 47% estimated vaccination coverage in immunocompetent adults ≥65 years. Based on these results, it was estimated that 26,000 adults would need to be vaccinated with PCV13

to prevent one case of IPD per year. Additionally, there were minimal indirect benefits to other patient populations, including those aged 19–64 years. Cost-effectiveness models estimated a very high cost ($200,000–500,000) per quality adjusted life years with continuation of the current recommendation versus a recommendation to administer PPSV23 alone. Limitations to the presented evidence included the limited follow-up time (only three years of data were analyzed) and low PCV13 vaccination uptake in immunocompetent adults. Furthermore, the analysis did not take into consideration vaccination hesitation, commonly known as the "anti-vax movement," a growing movement which may impact pneumococcal pediatric vaccination rates and pneumococcal burden in the coming years.

Updated pneumococcal vaccination recommendations are summarized in **Table 1**. Based on these findings, ACIP voted to remove PCV13 from the routine immunocompetent adult immunization schedule in November 2019. As some adults may still benefit, the decision to administer PCV13 vaccination should be based on shared clinical decision-making between patient and provider depending on the individual's risk for exposure and invasive disease. PCV13 is still routinely recommended as a one-time vaccination for adults ≥19 years with an immunocompromising condition, cerebrospinal fluid leak, or cochlear implant.[8] Additionally, a single dose of PPSV23 is still routinely recommended for all adults at age 65.

Shared Decision-Making: Who Should Still Receive PCV13 At Age 65?

Some adults may be at higher risk for exposure to PCV13 serotypes or at higher risk for complications based on certain factors, such as local pediatric vaccination rates or underlying medical conditions. The CDC provides guidance for shared clinical decision-making based on an individual's risk.

The CDC recommends considering regularly offering PCV13 to the following individuals:

- Those residing in a nursing home or other long-term care facilities
- Those residing in settings with low pediatric PCV13 uptake
- Those traveling to settings with no pediatric PCV13 program
- Those with chronic heart, lung, or liver disease; diabetes; or more than one chronic medical condition
- Those with alcoholism or those who smoke cigarettes

Table 1. Updated ACIP Recommendations for Pneumococcal Vaccination in Individuals ≥19 years

Patient Population	Age Group		Total Number of doses of PCV13 or PPSV23
	19–64 years	≥65 years	
Immunocompetent individuals	PCV13: none	PCV13 based on shared clinical decision-making; if administered give PCV13 first and PPSV23 ≥1 year after PCV13	PCV13: 0 or 1 dose
	PPSV23: none	PPSV23 x 1 dose	PPSV23: 1
Immunocompetent individuals with alcoholism; chronic liver, heart, or lung disease; diabetes mellitus; or smoking cigarettes	PCV13: none	PCV13 based on shared clinical decision-making; if administered give PCV13 first and PPSV23 ≥1 year after PCV13	PCV13: 0 or 1 dose
	PPSV23 x 1 dose	PPSV23 x 1 dose, give ≥5 years after any previous PPSV23 prior to age 65	PPSV23: 2 doses
Immunocompetent individuals with cochlear implant(s) or cerebrospinal fluid leaks	PCV13 x 1 dose	PCV13 x 1 dose if no previous PCV13 vaccination	PCV13: 1 dose
	PPSV23 x 1 dose, give ≥8 weeks after PCV13	PPSV23 x 1 dose, give ≥8 weeks after PCV13 and ≥5 years after any previous PPSV23 prior to age 65	PPSV23: 2 doses
Immunocompromised individuals*	PCV13 x 1 dose	PCV13 x 1 dose if no previous PCV13 vaccination	PCV13: 1 dose
	PPSV23 x 2 doses, give first dose ≥8 weeks after PCV13, give second dose ≥5 years after initial PPSV23	PPSV23 x 1 dose, give ≥5 years after any previous PPSV23 prior to age 65	PPSV23: 3 doses

*Includes those with anatomic or functional asplenia, sickle cell disease/hemoglobinopathies, chronic renal failure or nephrotic syndrome, congenital or acquired immunodeficiencies, iatrogenic immunosuppression, generalized malignancy, Hodgkin disease, leukemia, lymphoma, multiple myeloma, HIV infection or solid organ transplant

HERPES ZOSTER VACCINATION

Background

Herpes Zoster (HZ) is another infection that affects elderly and immunocompromised patients due to decreased immune control of the virus. It is caused by reactivation of primary Varicella Zoster Virus (VZV) infection in the neuronal ganglia leading to a painful vesicular rash along one or more dermatomes. According to the CDC, there are approximately 1 million cases of HZ per year in the United States.[9] Many studies have shown that the incidence of HZ has increased over time.[10,11] Harpaz and colleagues found that incidence has continued to rise from the 1990s to the most recent decade. The incidence per 1,000 persons has increased from 2.5 in 1993 to 6.1 in 2006 to 7.2 in 2016.[10] HZ is a vaccine preventable illness that carries significant morbidity and cost implications for the healthcare system. The most well-known complication, post-herpetic neuralgia (PHN), can persist for years after initial infection and is often refractory to traditional analgesics. Furthermore, treatments such as tricyclic antidepressants and gabapentin carry significant risks of toxicity in the elderly patient population that is most susceptible to this condition. Other potential complications include bacterial superinfection of the skin, HZ opthalmicus, acute retinal necrosis, HZ oticus, and meningitis/encephalitis. It is estimated that the total cost of HZ is 5 billion dollars annually in the United States.[12]

Historical ACIP Recommendations for Herpes Zoster Vaccination

Zoster Vaccine Live (ZVL, [Zostavax, Merck and Co., Inc]) was licensed in 2006 as a single subcutaneous dose and was recommended by the ACIP for use in immunocompetent adults aged ≥60 years. FDA approval was based on the Shingles Prevention Study, which was a double-blinded, multi-centered, randomized controlled trial. The study followed subjects for three years and compared incidence of HZ infection and PHN in patients receiving ZVL or placebo. For patients between 60-69 years of age, there were statistically significant decreases in both conditions in those who received ZVL compared to placebo: 66% decrease in HZ and 66% decrease in PHN.[13] However, post-marketing studies have shown marked decreases in effectiveness against HZ over time, especially in older subjects (age > 60 years old).[13] The incidence of injection site reactions such as erythema and pain was 35.8% and 34.5%, respectively. Systemic adverse events were similar in the vaccine group compared to placebo (24.7% vs 23.7%).[13] Furthermore ZVL is a live vaccine and therefore contraindicated in many immunosuppressed populations, which are one of the highest risk groups for developing HZ.

Updated ACIP Recommendations for Herpes Zoster Vaccination

Recombinant Zoster Vaccine (RZV, [Shingrix, GlaxoSmith-Kline]) was approved in October of 2017 as a two-dose intramuscular injection administered at 0 and 2–6 months. This inactivated vaccine contains a new VZV glycoprotein E antigen combined with adjuvant $AS01_B$ to promote humoral immune response and has the potential to be used in immunocompromised populations. RZV quickly became the preferred HZ vaccine in the adult immunization schedule in January of 2018.[15] This change was driven primarily by the increased effectiveness in primary prevention of HZ as well as superior sustained protection post-vaccination. Two multi-national, randomized, placebo-controlled clinical trials led to approval of RZV. The ZOE-50 study showed overall efficacy rates of 97.2%.[16] Furthermore, in older subjects aged 60–69 years old, it maintained efficacy at 97.4%. No significant differences were seen in regards to age. ZOE-70 enrolled patients over the age of 70 and showed an 89.8% decrease in incidence of HZ.[17] Pooled data from these studies showed an overall 91.2% decrease in PHN in those in the active treatment arm. Data from these studies demonstrate that RZV vastly outperforms ZVL across all age groups. Long-term efficacy has yet to be established, as the published data only includes 36 months of follow-up. The ZOE-50 study plans to complete a total follow-up of 60 months, but this data has not been published at the time this article was written.

Although RZV has shown superior efficacy, there is a higher incidence of adverse drug reactions likely related to the increased immunogenicity of the adjuvant. For example, in ZOE-50, a total of 81.5% of participants in the RZV arm reported injection site reactions.[16] While most of these reports were mild to moderate in nature, 9.5% had grade 3 reactions. In terms of systemic reactions, incidence was 66.1% with myalgia (46.3%) and fatigue (45.9%) as the most common in RZV-vaccinated subjects. However, median duration of reactions was less than 4 days. Despite the higher incidence of adverse reactions when compared to ZVL, the remarkable efficacy of RZV in preventing HZ and PHN warrants its place as the preferred HZ vaccine.

In addition to increased rate of side effects, availability of the vaccine has been a barrier to vaccination. The supply of the vaccine has been sporadic, and it is frequently under allocation limits. This presents a challenge for patients who have received one dose but have not received the second dose in the series. If more than 6 months have elapsed after the initial dose, there is no need to restart the series. RZV is recommended for patients previously vaccinated with ZVL and can be given simultaneously at different anatomic sites with other vaccines.[15]

Of note, ACIP currently provides no recommendation on the use of RZV in patients with high levels of immunosuppression, including those on chronic steroids (≥20 mg of prednisone equivalent per day), those who have received a transplant, or persons living with HIV due to insufficient data in these populations.[15] A recent phase 3 clinical trial in patients with renal transplant has shown sufficient rates of immunogenicity and a similar adverse event profile.[18] As new data becomes available for immunocompromised patients, these recommendations may change.

CONCLUSION

ACIP's recommendations for pneumococcal and herpes zoster vaccination have recently been updated. For pneumococcal vaccination, ACIP now recommends shared clinical decision-making rather than routine administration of PCV13 in immunocompetent individuals ≥65 years. A single dose of PPSV23 is still routinely recommended for all adults at age 65, and a one-time dose of PCV13 should still be administered for adults ≥19 years with an immunocompromising condition, CSF leak, or cochlear implant.

For herpes zoster vaccination, the ACIP now recognizes RZV as the preferred zoster vaccine for all eligible patient populations. RZV is preferred over ZVL due to higher efficacy and sustained protection over time and can be administered to patients who have previously received ZVL.

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Tetanus Vaccination 2020 and Collateral Protections against Pertussis and Diphtheria

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ABSTRACT

Tetanus is a life-threatening but vaccine-preventable disease caused by the toxin of the bacterium *Clostridium tetani* and is characterized by muscle spasms and autonomic nervous system dysfunction. It is prevented through vaccination with tetanus toxoid, but because the causative agent is widespread in the environment, eradication is impossible. Therefore, efforts to reduce incidence are aimed at reaching elimination, rather than eradication. This article reviews the pathogenesis, clinical manifestation and treatment of tetanus, and summarizes all recommendations from CDC's Advisory Committee on Immunization Practices (ACIP) regarding prevention and control of tetanus in the United States.

KEYWORDS: tetanus, tetanus vaccine, tetanus prophylaxis, tetanus immunoglobulin

INTRODUCTION

Tetanus is a serious and often fatal infection that affects the nervous system. It is characterized by generalized painful muscle spasms particularly in unvaccinated or incompletely vaccinated people. The disease is caused by a toxin-producing gram-positive anaerobic bacteria, *Clostridium tetani*, which is widely present in the surrounding environment, particularly in soil, dirt, and dust.

Tetanus is still prevalent in many developing countries. The disease can be prevented through vaccination but because the *C. tetani* spores are ubiquitous, it can never be eradicated. Due to the success of the US tetanus immunization program diphtheria – a disease of the upper respiratory tract and sometimes skin due to toxigenic strains of Corynebacterium diphtheriae biotype mitis, gravis, intermedius or belfanti – is nearly unheard of in the US, although the disease continues to cause illness globally and there have been outbreaks reported in recent years.

PERTUSSIS

Pertussis – "whooping cough" due to Bordetella pertussis – can be a life-threatening disease in infants with small airways and is endemic worldwide, including the US and other countries, with high vaccination rates. Disease in adults presents as a protracted cough with paroxysms that may be followed by vomiting. Coughing paroxysms may eventually become less intense but may recur with subsequent respiratory infections. Childhood vaccinations given since the 1940s helped to reduce infant mortality but would wear off by adulthood.

ELIMINATION STRATEGIES

The primary strategy to control and prevent these diseases is through elimination instead of eradication. The vaccination schedule is based on the tetanus component.

Tetanus is a leading cause for neonatal death in the developing world.[1]

The tetanus toxoid (TT) vaccines were first introduced in the United States in the mid-1940s. After that, the incidence of reported tetanus declined by >98%, from 0.39 per 100,000 population in 1947, when national reporting began, to 0.01 per 100,000 population by 2016.[2] The CDC reported 264 cases of tetanus in the United States between 2009 and 2017, 23% were in patients ≥65 years of age and only 13% were individuals younger than 20 years. The majority of new cases of tetanus occur in resource-limited countries with an estimated 48,000 to 80,000 deaths occurring from tetanus worldwide in 2016.[3]

PATHOPHYSIOLOGY

Humans become infected through wound contamination with *C. tetani* spores, which are durable and can survive for prolonged periods and germinate under the right environment (i.e. less vascularized necrotic tissue) to toxin-producing bacteria. The toxin is extremely potent and even deadly in small amounts. Once tetanus toxin invades the nerve cell, it can no longer be neutralized by the toxoid. The toxin can then move via retrograde axonal transport into the spinal cord and brain, where it accumulates and prevents the release of inhibitory neurotransmitters, resulting in overexcitation of the nervous system. This clinically manifests as painful muscle spasm and rigidity, increased muscle tone, and widespread autonomic instability.

Tetanus is a non-communicable disease and it is safe to come in close contact with someone that is affected by tetanus.

Tetanus is commonly acquired through septic burn wounds, animal bites and scratches, fractures, contaminated surgical instruments, lacerations, eye injuries, gunshot wounds, piercings and other puncture wounds. All of the above mechanisms have common predisposing factors, which include devitalized and dead tissue, foreign bodies and localized ischemia.

Tetanus can also manifest through the same pathophysiology in neonates from infected umbilical stump, obstetric patients after septic abortions, post-surgical patients with bowel necrosis, infected diabetic foot ulcer patients, and IV drug users.

The incubation period of tetanus is approximately 8 days but ranges from 3 to 21 days.

The most common and severe clinical form of tetanus is generalized tetanus. Rarely, tetanus presents with tonic and spastic muscle contractions in one extremity or body region which is localized tetanus. Patients with injuries to the head or neck may present with cephalic tetanus, involving initially only cranial nerves. Neonatal tetanus occurs as a result of the failure to use aseptic techniques in managing the umbilical stump in offspring of mothers who are poorly immunized. Severity of disease can range from grade 1 (mild trismus and/or general spasticity), to grade 2 (moderate trismus and general spasticity, with dysphagia and respiratory embarrassment), to grade 3 (severe trismus, severe and prolonged spasms, respiratory difficulties and sympathetic overdrive).

MANAGEMENT

Unfortunately, little evidence exists to support any particular therapeutic intervention in tetanus. Management includes early wound debridement, halting the toxin production, neutralization of the unbound toxin through post-exposure vaccination, control of muscle spasms, and general supportive care including airway management. Antibiotics are universally recommended, although they may play a minor role, and it is of vital importance to emphasize that unless adequate wound debridement is performed, antimicrobial therapy may fail. Metronidazole is the preferred treatment and should be given for a total of 7 days but penicillin is a safe alternative. Multiple other agents can be used such as doxycycline, macrolides, clindamycin, vancomycin, and chloramphenicol; however, the data on these agents is based upon in vitro susceptibility. Since tetanus toxin is irreversibly bound to tissues, much emphasis is placed on neutralizing the toxin before it enters the nervous system. Human anti tetanus immunoglobulin (HTIg) is the treatment of choice. The CDC recommends a single dose of 500 units intramuscularly with part of the dose infiltrated around the wound. Many studies have explored the efficacy of intrathecal immunoglobulin, but the evidence for its benefit is not concrete. All patients with tetanus should receive active immunization with a full series given immediately upon diagnosis. The tetanus toxoid should be given at a separate site from immunoglobulin administration.

Benzodiazepines remain the backbone of treatment regimens for tetanus, and the standard therapy for controlling muscle spasms. Diazepam is the most popular and has been used widely but other benzodiazepines are as effective. The use of magnesium sulfate has also been established since the 1980s due to its effect on reducing autonomic instability and controlling muscle spasms. Several studies concluded the beneficial effects of high dose magnesium sulfate infusion in tetanus, but it may be inadequate as sole therapy in patients with severe disease. Several other drugs which have been reported to be useful are labetalol, clonidine, morphine sulfate, intrathecal baclofen, dantrolene, and vitamin C. Despite all these interventions, the reported fatality rate ranges from 12–53%

VACCINE SCHEDULES

In the US, diphtheria-tetanus-acellular pertussis (DTaP) vaccine is routinely administered to children at 2, 4, and 6 months, followed by boosters at 15–18 months and 4–6 years. Single booster dose of a vaccine containing tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) is recommended for 11- to 12-year-olds and every ten years after that. In 2020, ACIP released new recommendations allowing either Tdap or Td to be used as the booster or for wound management while previously only Td was recommended.[5]

Individuals who have not been previously vaccinated against tetanus should complete a series of three tetanus and diphtheria toxoid vaccines, which includes at least 1 Tdap dose. The preferred schedule is 1 dose of Tdap, followed by 1 dose of either Td or Tdap at least 4 weeks afterward, and 1 dose of either Td or Tdap 6–12 months later.

In 2011, when ACIP first considered administration of Tdap during pregnancy, safety data on women and their infants were limited. However, additional evidence continues to be reassuring for mother and child, with no reported increase in adverse events including major malformations, stillbirth, preterm birth, or small for gestational age. Pregnant women should get Tdap during the early part of the 3rd trimester of every pregnancy.

ACIP has recommended administering tetanus toxoid containing vaccine and tetanus immune globulin (TIG) when indicated as part of standard wound management to prevent tetanus. For patients who have received fewer than three doses or an unknown number of doses of a tetanus toxoid-containing vaccine, tetanus immunization should be administered. For patients with clean minor wounds who have completed 3-dose primary tetanus vaccination series, another dose should be given if the last dose was given 10 or more years ago. For patients with dirty wounds (such

as, but not limited to, wounds contaminated with dirt, feces, soil, or saliva; puncture wounds; avulsions; wounds resulting from missiles, crushing, burns, or frostbite) who have completed 3-dose primary tetanus vaccination series, another dose should be given if the last dose was given five or more years ago. If there is any doubt about whether or not an adult completed the primary series, three doses of Td or Tdap (with Tdap given for at least one of the doses) should be administered; the first dose and second dose should be separated by four weeks and the third dose should be given 6 to 12 months later. The pertussis component may dwindle after 3-4 years as data show the vaccine fully protects 4 in 10 individuals 4 years after receiving Tdap. For travelers or during pertussis outbreak settings it is safe to administer Tdap as early as 2 years after the prior dose.

HUMAN TETANUS IMMUNE GLOBULIN

In addition to tetanus immunization, human tetanus immune globulin (250 units intramuscularly) is indicated in unvaccinated or incompletely vaccinated individuals who have sustained a wound that is more severe than a clean and minor wound (eg, wounds contaminated with dirt, feces, soil, or saliva; puncture wounds; avulsions; wounds resulting from missiles, crushing, burns, or frostbite).

People with human immunodeficiency virus (HIV) infection regardless of their CD4 count or with severe immunodeficiency who have contaminated wounds should also receive human tetanus immune globulin, regardless of their immunization status.

Appropriate tetanus prophylaxis should be administered as soon as possible following a wound but should be given even to patients who present late for medical attention. This is because the variable incubation period which ranges from 3 to 21 days (median: 7 days), with extremes of 1 day to several months.

Tetanus toxoid is one of the most extensively used vaccines globally. Mild local reactions (i.e., redness, pain and tenderness, and mild swelling) are common while more systemic reactions, such as fever, malaise, lymphadenopathy are less common but might still occur. Although there is a slight increase in injection site events with decreasing interval since a previous immunization, Tdap can be safely administered at intervals of > or = 18 months since a previous TD/Td vaccine.[6] Severe reactions, including neurologic complications (e.g., peripheral neuropathy, particularly brachial plexus neuropathy, Guillain-Barré syndrome, and acute encephalopathy) and hypersensitivity reactions (anaphylaxis, and angioedema) are rare. Arthus reactions – severe local and sometimes generalized vasculitic reactions - are now only rarely reported with newer tetanus vaccine preparations. ACIP recommends that persons who have experienced an Arthus reaction following a dose of tetanus toxoid or diphtheria toxoid–containing vaccine should not receive a tetanus toxoid–containing vaccine more frequently than every 10 years, even for tetanus prophylaxis as part of wound management.

CONCLUSION

Tetanus is a lethal infection, but vaccine preventable. Tdap offers protection against diphtheria and pertussis not only to children but also adults. All healthcare workers must emphasize and raise awareness of the importance of immunization. Protection against tetanus by vaccination is vital because there is no natural immunity against tetanus and no effective treatments exist. Inter-professional collaboration of physicians, nurses other clinical practitioners and pharmacists together with public health officials can place particular emphasis on education regarding the importance of up-to-date vaccination and reduce the morbidity and mortality of tetanus worldwide.

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An Update on Meningococcal Vaccination

JOSEPH M. GARLAND, MD

ABSTRACT

Neisseria meningitidis bacterial infection can cause severe life-threatening meningitis. Individuals who survive may be left with profound sequelae. In epidemic regions such as the meningitis belt of Africa, the case rate is drastically higher than in nonepidemic regions and is due to distinct outbreak serogroups. Two highly effective conjugate meningococcal vaccine against serogroups A, C, W and Y are licensed and indicated for prevention in childhood vaccination schedules and for travelers to outbreak regions. In the US, meningococcus serogroup B is the main cause of outbreaks, in areas with crowding such as college dorms. It has taken over 40 years to develop a meningitis type B vaccine and now there are 2 brands available for children and teens. All college-bound individuals should complete schedules of both conjugate ACWY serotypes and meningitis B vaccine series. This paper reviews details on who to vaccinate and how to use the currently available meningococcal meningitis vaccines.

KEYWORDS: meningitis vaccine, *Neisseria meningitidis*, serogroups ACWY, meningitis serogroup B, conjugate meningococcal vaccination

Neisseria meningitidis causes a wide range of clinical presentations, from asymptomatic carriage to severe life-threatening meningitis. When it presents with clinical disease, *N meningitidis* causes meningitis in over 50% of cases; other presentations include pneumonia and bacteremia. Person-to-person transmission of bacteria occurs through close personal contact with respiratory secretions or saliva of infected persons. Colonization is common – at any given time 5–10% of the population may be carriers of the organism. In contrast, invasive disease is rare in non-epidemic areas, occurring at a rate of 0.5 to 10 cases per 100,000. However, in epidemic regions such as the meningitis belt of Africa, the case rate can be drastically higher, up to 1,000 cases per 100,000, particularly during peak season. There are six major serogroups associated with human disease: A, B, C, X, Y, and W-135. *N meningitidis* is found worldwide, with some regional differences in serogroup distribution and prevalence.[1,2,3]

Though prevalence of clinical disease is low in non-epidemic regions, the severity of meningococcal disease when present, and the high mortality associated with *N meningitidis* meningitis, have led to recommendations for vaccination of key populations. Two types of meningococcal vaccines are available in the U.S. currently, one type covering serogroups A, C, Y, and W-135, and the other covering serogroup B. (**Table 1**)

For serogroups A, C, Y, and W-135, two similar vaccines are available: MenACWY-D (Menactra) and MenACWY-CRM (Menveo). Both are conjugate vaccines. The previously available quadrivalent polysaccharide vaccine (MPSV4, or Menomune) was discontinued in August 2017. The conjugate A, C, Y, and W-135 vaccines are approved for age 9 months and older (MenACWY-D) or 2 years and older (MenACWY-CRM) through the age of 55 years, though most authorities advise off-label usage if otherwise indicated in individuals over

Table 1.

VACCINE	TRADE NAME	AGE OF VACCINE INITIATION	DOSE	ROUTE	INTERVAL SINCE FIRST DOSE	BOOSTER
Conjugate Meningococcal A,C,W and Y vaccine	Menveo	2 mo	0.5 mL	IM	0,2,4, 10 mo	If at continued risk
		7–23 mo	0.5 mL	IM	0, 3 mo (2nd dose administered in 2nd year of life)	
		≥ 2 y	0.5 mL	IM	1 dose if traveling, then 2 doses given 8 weeks apart	
	Menactra	9–23 mo	0.5 mL	IM	0, 3 mo	If at continued risk
		≥ 2 y	0.5 mL	IM	1 dose	
Meningitis B vaccine	Trumenba	10–25 y	0.5 mL	IM	0, 1–2, 6 mo or 0, 6 mo The 3-dose schedule is preferred for groups at increased risk where more rapid protection is desired	None
	Bexsero	10–25 y	0.5 mL	IM	0, ≥ 1 mo	None

the age of 55 as, with the withdrawal of MPSV4, there is no approved vaccine for this age group. In polysaccharide vaccines only the sugar part of the bacteria, the capsule, is included as the antigen to stimulate the immune response. In conjugate vaccines the sugar is joined to a carrier protein to trigger a stronger and more long-lasting response. With the quadrivalent conjugate vaccines, protective antibody levels against all four serogroups develop within 10–14 days after vaccination, and protection of 90–95% is estimated. The duration of protection is shorter in children younger than 5 years of age, but generally considered to be 5 years in adolescents and adults. Conjugate vaccines carry the advantage over the older polysaccharide vaccine of eliciting stronger immunologic memory (generally with recommended revaccination only every 5 years in adults), a reduction in nasopharyngeal carriage, and more effective interruption of transmission and establishment of population protection.[3,4]

Meningitis B vaccinations have been more recently developed, as vaccine development against this serogroup was so challenging that it took over 40 years. The serogroup B polysaccharide resembles a human neural cell adhesion molecule, which raised concern about inducing autoimmunity. Outer membrane vesicle vaccines were developed and effective in outbreak settings, but were limited against the diversity of worldwide B strains. The current approved meningitis B vaccines in the US are recombinant protein-based and were developed through "reverse vaccinology" to identify target preserved proteins, and are widely protective against most meningitis B strains. Both approved in 2015, MenB-4C (Bexsero) and MenB-FHbp (Trumenba) are recommended as equivalent by the ACIP. They are approved for usage in individuals ages 10 through 25.[4] Meningitis B accounts for 40% of the meningitis cases in the US, and 10 university campus outbreaks were associated with this serogroup between 2013 and 2018.[5]

The ACIP now recommends meningitis vaccination routinely to adolescents and meningitis ACWY vaccination routinely in children between the ages of 11 and 18. MenACWY vaccination is administered as a two-dose series, separated by a minimum of 8 weeks, starting at 11–12 years of age, with a booster at age 16. Meningitis B vaccination is recommended, based on shared clinical decision-making, between the ages of 16 and 23 years (preferred ages 16–18). MenB-4C is administered as a 2-dose series separated by at least 4 weeks; MenB-FHbp is administered as a two-dose series separated by at least 6 months (a third dose at least 4 months later is recommended if dose #2 is administered prematurely). Patients should complete the series with the same vaccine as the original dose. Common reactions include pain and redness at the injection site and mild fever for 1 to 2 days. [6,7,8,9]

Other populations are encouraged to pursue vaccination due to increased risk. Vaccination against MenACWY is recommended in patients with functional or anatomic asplenia, patients with HIV infection, persistent complement deficiency, or use of a complement inhibitor (e.g. celuizumab, ravulizumab). It is also recommended in first-year college students and military recruits who were not previously vaccinated. MenACWY vaccination is additionally recommended in travelers to countries with high risk of sporadic outbreaks, particularly the so-called "meningitis belt" across sub-Saharan Africa, which includes a number of countries as well as parts of other African nations. (**Table 2**) Further, all persons entering Saudi Arabia for the Hajj and Umrah **require** MenACWY due to outbreak risk related to crowding. MenB vaccination is recommended outside of the standard dose interval described above in the setting of anatomic or functional asplenia, complement deficiency, and use of complement inhibitors. [6,7,8,9] During outbreak settings, vaccination of affected populations is recommended. A number of outbreaks in men who have sex with men in the past 10 years have led municipalities to offer MenACWY vaccination to these populations as well. [10]

Table 2.

Countries in the "Meningitis Belt"	Other African nations with increased meningococcal outbreak risk
Senegal	Uganda
Gambia	Mauritania
Guinea-Bissau	Mali
Guinea	Burkina Faso
Sudan	Côte d'Ivoire
South Sudan	Ghana
Eritrea	Togo
Ethiopia	Benin
Northwest Kenya	Nigeria
	Niger
	Cameroon
	Chad
	Central African Republic,
	Democratic Republic of Congo

Adapted from CDC website: www.cdc.gov/meningococcal

Though a rare disease, meningococcal disease can be associated with high morbidity and mortality. With the availability of effective vaccinations against most serogroups, including effective vaccines for serogroup B added in 2015, we have a new ability to prevent outbreaks and individual infections. Clinicians should remember to offer these vaccinations to all adolescents, but also remember key higher risk populations, including travelers to sub-Saharan Africa, individuals embarking on the Hajj or Umrah, and immunocompromised patients including people living with HIV. Meningococcal disease prevalence in the US is decreasing, in part due to increased vaccination, but further progress can be made by remembering and counseling adolescents, their parents, and high-risk individuals.

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Hepatitis A and B Vaccination in the United States

MARTHA C. SANCHEZ, MD

ABSTRACT

Use of hepatitis A vaccine is a main component of travel vaccination practices. In the United States, fluctuations in the number of annual hepatitis A infections have occurred recently due to large outbreaks related to imported foods and urban transmission among homeless individuals, warranting consideration for wider local use of hepatitis A vaccine.

Hepatitis B vaccine is indicated for all adults, and especially healthcare workers. Since 1992, it has been administered at birth. A new novel hepatitis B vaccine given in two doses one month apart is available and has increased efficacy in adults. This article reviews the complete administration of these hepatitis vaccines.

KEYWORDS: hepatitis A, hepatitis B, immunizations, healthcare workers, heplisav-B

HEPATITIS A

Hepatitis A virus (HAV) is a nonenveloped positive strand RNA virus, member of the Picornavirus family, that is mainly transmitted through fecal-oral route and exposure to contaminated food and water sources. It commonly causes a self-limited inflammatory response in the liver that is associated with generalized symptomatology, but in rare cases it may progress to fulminant hepatitis and liver failure.[1] Although the average number of annual HAV infections reported to the Centers for Disease Control (CDC) recently has declined substantially compared to the year 2000, fluctuations have occurred in the last 20 years because of large outbreaks related to imported foods, people who use drugs, experience homelessness and men who have sex with men.[2]

Vaccines

There are two licensed Hepatitis A antigen vaccines available in the Unites States for individual 12 months and older, HAVRIX® (manufactured by GlaxoSmithKline) and VAQTA® (manufactured by Merck & Co., Inc). The schedule for HAVRIX® is 0, 6–12 months and for VAQTA® 0, 6–18 months.[3] Both vaccines provide high immunogenicity-inducing protective antibody levels in 94%–100% of adults one month after the first dose, and 100% one month after the second dose. Similar rates of neutralizing antibodies are found in children and adolescents. Protective antibody levels appear to persist beyond 20 years in healthy individuals.[1]

Twinrix® (manufactured by GlaxoSmithKline), a combined hepatitis A and hepatitis B vaccine, was first licensed by the Food and Drug Administration (FDA) in 2001 on a 3-dose schedule (0, 1, and 6 months) for vaccination of persons aged ≥18 years.[4] The efficacy of Twinrix has been found to be comparable with existing single antigen hepatitis vaccines at 1 month after completion of series. At an alternate 4-dose schedule, Twinrix doses can be administered at 0, 7, and 21 to 30 days, followed by a dose at 12 months. This alternate dosing may be useful when vaccination with Twinrix has been initiated and travel or other potential exposure is anticipated before the second dose.[5]

Indications

In 1999 the Advisory Committee on Immunization Practices (ACIP) recommended vaccination against hepatitis A routinely to children at age 12 to 23 months living in communities with high rates of disease, which led to a 79% decline of cases in states with prior elevated rates in 2004 compared to 1996.[6] In 2006, ACIP extended the recommendation of routine hepatitis A vaccination to children nationwide.

Other groups advised for HAV vaccination due to increased risk of exposure include: men who have sex with men (MSM), users of injection and non-injection drugs, persons with clotting-factor disorders, persons with occupational risk of infection, persons with chronic liver disease, persons traveling to or working in countries that have high or intermediate hepatitis A endemicity.[1]

Preexposure prophylaxis with hepatitis A vaccine is also indicated for unvaccinated persons who are household members and other close personal contacts of adopted children newly arriving from countries with high or intermediate hepatitis A.[7] The first dose of the HAV vaccine should be given ideally 2 or more weeks before the arrival of the adoptee. For infants 6–11 months of age that are at increased risk for HepA exposure, a single dose of HAV vaccine may be given; this dosage will not be counted toward the routine 2-dose series.

Given the higher risk for HAV infection and severe infection-associated outcomes in persons experiencing homelessness, in October 2018 the ACIP advised that all persons aged 1 year and older in this group be routinely immunized

against HAV.[8] Immunity towards HAV in this population is expected to reduce the risk of large-scale, person-to-person outbreaks, but possible barriers to vaccination include limited access to care and insurance coverage among persons experiencing homelessness.

Post-exposure prophylaxis has been shown to be beneficial for persons exposed to HAV within a 2-week period; it is favored over the immunoglobulin due to induction of active immunity, longer duration of protection, ease of administration, and greater acceptability and availability.[9]

Adverse Effects

Pain at the injection site (56%–67%), headache (14%–16%), and malaise (7%) are the most common side effects reported in adults. No serious adverse events have been definitively related to the hepatitis A vaccine.[1]

Contraindications

Hepatitis A vaccine should be avoided in those with a history of severe allergic reaction such as anaphylaxis to any component of the vaccine.

Pregnancy

The risk to the fetus when the vaccine is given during pregnancy has not been determined; since the vaccine is inactivated, it is suspected to be low.[10]

Safety

The vaccine may be given to immunocompromised patients, since it is inactivated. In this population, efficacy may be lower depending on the degree of immunosuppression.

Hepatitis A Immunoglobulin

GamaSTAN S/D is available in the United States, with recommended dosing of 0.1 mL/kg for up to 1 month of planned travel duration and 0.2 mL/kg for up to 2 months has been shown to decrease HAV infection by 90%. It may be given, in conjunction to the HepA vaccine, at separate anatomic sites, within 2 weeks potential exposure to HAV for: adults aged >40 years, immunocompromised persons, those with chronic liver disease, or other chronic medical conditions. Persons may receive the hepatitis A immunoglobulin alone if they are <12 months of age, are allergic to a component of the vaccine or choose not to receive the vaccine.[11] Immunoglobulin cannot be administered simultaneously with MMR.

HEPATITIS B

Hepatitis B (HepB) is a DNA virus of the Hepadnavirus family that is an important cause of chronic liver disease worldwide, which may lead to liver cirrhosis and hepatocellular carcinoma. It is transmitted through percutaneous or mucosal exposure to infectious blood or body fluids. The liver is the main site of infection, causing asymptomatic and symptomatic disease. The primary infection is usually self-limited in immunocompetent adults, causing chronic infection in about 5% but it may be as high as 30–90% in children <5 years old. In the US, the rate of reported acute hepatitis B virus infections declined 88.5% since recommendations for HepB vaccination were first issued, from 9.6 cases per 100,000 population in 1982 to 1.1 cases per 100,000 population in 2015.[12,13]

Vaccines

Two single antigen vaccines against hepatitis B are available in the United States, Recombivax HB® (Merck & Co., Inc., Whitehouse Station, New Jersey) and Engerix-B®(GlaxoSmithKline Biologicals, Rixensart, Belgium). Either should be administered at 0, 1, and 6 months, but alternate schedule of 0, 2 and 4 months or 0, 1 and 4 months will provide similar response. After the first dose, 30–50% of healthy adults will have protective antibody levels, 75% after the second dose and 90% after the third. An accelerated schedule may be given at 0, 7, and 21 days, followed by a booster at 12 months. The hepatitis B virus (HBV) vaccine after the completed vaccination series provides protection for about 20 years and possibly lifelong.

A combined inactivated hepatitis A and hepatitis B vaccine (Twinrix, GlaxoSmithKline) is available for those 18 years and older to be given 0, 1 and 6 months or an accelerated schedule at 0,7, 21–30 days with a booster at 12 months.

On February 2018, Heplisav-B (HepB-CpG), a single-antigen HepB vaccine with a novel immunostimulatory sequence adjuvant was recommended for the prevention of HBV in persons aged ≥18 years. This vaccine is administered as 2 doses, 1 month apart, and has improved immunogenicity with a similar safety profile to Engerix-B®.[14,15] Seroprotective antibody to hepatitis B surface antigen (anti-HBs) levels were achieved in 90.0%–100.0% of subjects receiving 2 doses of HepB-CpG, compared with 70.5%–90.2% of subjects receiving 3 dose series of Engerix-B.

The same vaccine formulation should be used to complete the series, although vaccination should not be deferred if same vaccine manufacturer is not available or unknown.[16]

Indications

HepB vaccination is universally indicated within 24 hours of birth for medically stable infants weighing ≥2,000 grams. In addition, routine vaccination is advised for unvaccinated children and adolescents aged <19 years, as well as adults at risk for HBV infection – all healthcare workers, sexual exposure to hepatitis B, history of current or recent injection drug use, risk for infection by percutaneous or mucosal exposure to blood, persons with chronic liver disease, persons with human immunodeficiency virus infection, incarcerated persons – and those requesting protection from HBV without acknowledgment of a specific risk factor.[17]

International travelers to countries with high or

intermediate levels of endemic HBV infection (HBsAg prevalence ≥2%) should be vaccinated against HBV, particularly healthcare workers, disaster relief personnel, receipt of medical care, sexual activity, intravenous drug use, tattooing, among others.

Postvaccination serologic testing 1–2 months after the final dose of vaccine is recommended for certain persons following vaccination (e.g., hemodialysis patients, HIV-infected and other immunocompromised persons, healthcare personnel, and sex partners of HBsAg-positive persons). Revaccination may consist of administration of a second complete HBV vaccine series using any of the available vaccines. Administration of more than two complete HBV vaccine series is generally not recommended, except for hemodialysis patients.[17]

Adverse events

Most common reported side effects are pain at the injection site >10%. Other reactions such as low-grade fever, myalgia, and headaches are rare (<1%). Mild adverse event, serious adverse event, or cardiovascular event in subjects that received HepB-CpG were 45.6%, 5.4%, and 0.27% compared to subjects receiving Engerix-B, 45.7%, 6.3%, and 0.14%, respectively.[14]

Contraindications

Hepatitis B vaccine should not be administered to those with a history of severe allergic reaction such as anaphylaxis to yeast or any other component of the vaccine.

Pregnancy

The vaccine contains a noninfectious hepatitis B surface antigen and the risk to the fetus when the vaccine is given during pregnancy is low. There is limited human data of vaccine-associated risks on HepB-CpG administered to pregnant women.

Immunoglobulin

HepB immunoglobulin may be administered in conjunction with the hepatitis B vaccines in patients after high-risk exposure with infected blood or body fluids within 24 hours of exposure.

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It's Not Only Vaccine Hesitancy; It's Also Physician Hesitancy

DANIEL B. BLATT, MD; STEVEN D. BLATT, MD; PENELOPE H. DENNEHY, MD

ABSTRACT

The danger of vaccine hesitancy is perhaps one of the most critical challenges we face as practitioners. This riveting narrative helps us find common ground and courage as it reaches into the hearts of those of us who have encountered parents who also want what's best for their child.

KEYWORDS: vaccine hesitancy, immunizations, measles, vaccine side effects, pediatrics

The patient is here. I've printed out the CDC Vaccine Information Statements.[1] I can recite the top reasons for vaccine hesitancy while in a deep sleep. I've been here before and know all the rebuttals.[2-4] I have 15 minutes to help this family see why it is so important to immunize their child. I knock and open the door. A smile crosses my face and I sit down next to the parents. We discuss football, the weather, child development, nutrition. "…and today the immunizations we will be giving…"

Their backs straighten and the seats subtly shift. A deep inspiration echoes throughout the room, as the rapport I had built dissipates with their next words. "We do not vaccinate our children. We do not believe in vaccines."

As a physician, I've prepared for this. I know the arguments in their arsenal. Religion? I'll tell them about how most religions have no restriction on immunizations.[5] Infringement on personal rights? I'll tell them it's their choice, but more importantly, their duty to protect their child. Vaccines have side effects, cause autism, have too many toxins? I'll counter with CDC recommendations, cite small percentages, show the large studies, and go through the ingredient list.[6-8] I will "science" my way to victory.

The points and counterpoints flow in a volley of dialogue. I know that I have made a rock-solid case. I now ask if we will be vaccinating today. The words of parental defiance are palpable as defeat paints my ears with each syllable. Reflexes kick in as I confront myself with the stages of grief.

I couldn't have just failed, I was right!

I should kick them out of my practice. Any parent who can't get over this nonsense shouldn't be allowed to put my other patients at risk or waste my time.

Maybe if I offer a delayed schedule they will listen. But I'm doing that anyway. It's not good medicine.

I should just give up. This is just too hard to do.

Maybe I need to change my approach. That couldn't be it. Maybe I was using the wrong words. No, I know I'm right. Where did I go wrong?

"The single biggest problem in communication is the illusion that it has taken place."[9]
(Attributed to George Bernard Shaw)

I was not listening. I was debating. I was making my point and not feeling what they felt. I used arguments that fell on deaf ears and ignored their fears because "I was right." I was the doctor, the pediatrician. What I was hearing was their reasoning, their thought processes. *I had the illusion that I was communicating.* What was really being said was, "We're scared."

Acknowledge parental fears

It is really easy to scare someone, but really hard to un-scare them. Only by acknowledging fears, can we begin to understand how they are generated and then hopefully begin discussing how to overcome them. The issue is not the science and the issue is not physician knowledge. The issue is not antivaccine misinformation which we cannot control. The issue isn't even that we as physicians lack the time and tools to successfully teach our patients why we are so passionate about immunizing every child.[3,10,11] Every position, including those of our patients and their parents, has an underlying basis. What is the basis for vaccine refusal?

Basis for vaccine refusal

Eighty-one percent of Americans cannot name a living scientist.[12] We view ourselves as scientists, but apparently our patients do not. There is a lack of scientific appreciation in our society and this affects scientific literacy or, in this case, medical literacy. A doctor's visit may be the only time a patient or a parent has the ability to speak directly with someone who knows the science behind vaccines. But tainting the doctor-patient relationship with scientific terminology is often an ineffective way to teach our patients. Many scientists (ie, physicians) do not teach nonscientists (ie, patients or parents) effectively. This is evident in the lack of understanding we as healthcare professionals see in our patients every day. If we cannot explain our thoughts in simple terms, then we can teach nothing.

But do simple explanations always work? Can our patients understand how vaccines work and still be hesitant? In short, yes. Knowledge may not be the only barrier. It's one that needs to be addressed, but this hurdle does not stand alone. Most parents can understand statistics if explained clearly enough. But if fear guides that parent, statistics will not provide solace. A parent may understand the risk of contracting a disease by not vaccinating, but that knowledge is overshadowed by the fear of negative effects attributed to vaccination. The parent reasons that by avoiding vaccines, they are avoiding negative effects of vaccines. However, what is discounted is the real cost of not vaccinating, which is exposure to a much larger risk of disease.[4,13]

Statistics don't assuage fears. In addition to knowledge and statistics, we need stories. We need stories because each individual child does not fit into a statistical model. Parents, however, can relate to a story. A 1% risk of an adverse effect means nothing to the parent of a child who knows a story of a child who has been negatively affected by vaccines. Stories are powerful. Stories from people familiar to us (or seem close to us, such as those strangers on the Internet), who believe they have been harmed by vaccines, are the most powerful of stories.

> *"Belief begins where science leaves off and ends where science begins."*[14] — Rudolph Virchow

Parents are influenced by these anecdotes and we must fill our armamentarium with factual tales of our own, tales based in science. For many, anecdotes supersede statistics. It is difficult to convey the absence of disease caused by immunizations. Immunizations have been so successful in eliminating serious disease that most patients and many physicians don't have the same intimacy with invasive infections as we did in the past.[15] We need to speak about our patient intubated in the ICU with influenza pneumonia. We need to show emotion when speaking about our fear that the child in front of us may contract measles and die. We need to show exactly and in no uncertain terms why we care about our patients and what we are afraid of if they do not get immunized. What are the stories you want to tell?

Instead of asking why they are not immunized, we need to ask about their fears. We cannot afford to be hesitant engaging in effective communication. Instead of regurgitating vaccine facts, we need to teach how vaccines work. Vaccine-hesitant parents aren't necessarily difficult. What's difficult is effective communication. What's difficult is building or continuing the doctor-patient relationship when "they're not listening." When we encounter a parent who just wants the best for their child, we need to say exactly why we also want what is best for the child and exactly what we are afraid of. It isn't only the parent who is hesitant; we as physicians must overcome our own hesitancy.

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Japanese Encephalitis Vaccine

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ABSTRACT

Travelers to 24 endemic countries in Asia may be at risk for Japanese encephalitis. The ACIP has recently expanded guidelines on the use of Ixiaro, the inactivated Japanese encephalitis vaccine. This article reviews the disease burden of Japanese encephalitis and the role of a travel clinic in guiding travelers to Asia regarding decision-making about the use of this highly protective vaccine.

KEYWORDS: Japanese encephalitis, Asia travel, Japanese encephalitis vaccine, flavivirus, pig farming

INTRODUCTION

Travelers may be at risk for Japanese encephalitis (JE) in 24 endemic countries in Asia. Japanese encephalitis is caused by a Flavivirus closely related to West Nile virus and is transmitted predominantly by *Culex* mosquitoes that feed from dusk to dawn.[1] The JE virus is maintained in nature by mosquitoes and animal hosts, mainly pigs and water birds. Infection risk is therefore highest in rural farming areas but is also present in urban and periurban areas in Asia.

JE is endemic in most of Asia and parts of the western Pacific region and is one of the most common causes of encephalitis in Asia. Transmission is seasonal in some areas – May to September in northern Asia and monsoon season-related in India and Southeast Asia – but can occur year-round in other geographic regions such as in Bali, where rice paddies, pig farms, birds and *Culex* mosquitoes are abundant.[1] JE has also been reported in the Torres Strait Islands in northern Queensland, Australia. Interestingly, the great demand for pork in Asia has led to relocation and establishment of pig farms closer to urban centers for ease of distribution.[2] This may allow for increasing evolution of movement of risk for JE virus. Travel clinic consultation can help individuals navigate the country-specific information taking into account transmission months that can be found in the CDC Yellow Book.[1] JE infection is uncommon in tourists, with an estimated risk of one in 200,000 per week of exposure, and <1% of infections result in symptomatic illness. However, symptomatic cases are associated with significant morbidity related to acute encephalitis and present with a wide range of neurological symptoms. Case fatality rate of symptomatic cases is up to 30%. Of those who survive, 30% to 50% report long-term neurological, psychological, and cognitive impairment including polio-like weakness and life-long seizure disorders:[1,2] severe cases are very severe. Travelers to JE-endemic areas should be advised to take precautions against mosquito bites, particularly from dusk to dawn. Vaccination should also be considered, and recommendations must take into account the risk of infection (country, urban vs. rural, farming areas, seasons, outdoor activities, trip duration, and repeated travel). The high risk of death and serious long-term sequelae from symptomatic infections and the cost of vaccines are other important considerations.

The Advisory Committee on Immunization Practices (ACIP) has modified their guidelines.[3] As a general rule, it recommends vaccination for travelers who plan to spend a total of one month in endemic areas during the transmission season. Given that some US cases occurred in short-term travelers – some with less than one week of unexpected exposure – duration may not be the best factor in decision-making about vaccination against JE for an individual traveler to Asia. This disease is rare but has significant consequences. We offer JE vaccine for persons traveling outside of major urban areas. Those who plan to return to Asia will benefit from vaccination against the cumulative risk. Those traveling for <1 month should consider choosing vaccination if spending time in rural areas; taking part in high-risk activities (e.g., farming, outdoor sporting activities); staying in accommodations without screens, bed nets, or air conditioning; or traveling to outbreak areas.[1] Vaccination is strongly recommended for expatriates planning to live in Asia for more than 6–12 months, even in urban areas, because they often travel extensively throughout the region for work and vacations.[3] The only JE vaccine available in the USA is an inactivated Vero cell culture vaccine, Ixiaro (Valneva). In 2009 it was licensed for use in those aged 17 years, and in May 2013 the license was extended to children aged 2 months. Primary immunization consists of two IM doses given on days 0 and 28, completed at least a week before departure. Each dose is 0.25 mL for children aged <3 years and 0.5 mL for those aged 3 years. For adults with ongoing exposure to JE a booster dose is recommended 1–2 years after the primary course. There is currently limited evidence about the need for boosters for those aged <18 years.

An accelerated schedule on day 0 and day 7 with a booster in 1 year has been shown to provide excellent protection and is approved for last minute travelers to risk regions who are ages 18 to 65, weighing seasonal risk and planned outdoor activity.[4]

Adverse reactions

Local reactions such as pain and swelling are reported in 1% of vaccine recipients. Systemic reactions include headache, myalgia, fatigue, and fever.

Contraindications

Ixiaro is contraindicated in persons who have had serious adverse reactions from any JE vaccines or any of the vaccine components (including protamine sulfate or formaldehyde). No preservatives, stabilizers, or antibiotics are added to the formulation. For the manufacturing process Ixiaro also contains bovine serum albumin (not more than 100 ng/mL), Vero host cell DNA (not more than 200 pg/mL), sodium metabisulfite (not more than 200 ppm), and host cell protein (not more than 100 ng/mL). Safety data in pregnant women are currently lacking. The risk of vaccination to mother and fetus really cannot be defined, so this is an undefined situation in terms of making a decision based on risk. Ixiaro use should generally be avoided during pregnancy or breastfeeding unless the high-risk travel cannot be avoided. Some pregnant women opt to have the vaccine after consideration of their travel needs and discussion of disease risk.

OTHER CONSIDERATIONS

- For travelers who have been vaccinated with the previously available mouse brain-derived JE vaccine (JE-Vax, Biken), there is currently insufficient evidence regarding the effectiveness and duration of protection from a single booster dose of Ixiaro. Until further data are available, these travelers should be given a primary two-dose course of Ixiaro.
- For adult travelers who do not have time to complete the two-dose primary course before departure, an accelerated course of two doses on days 0 and 7 may be considered.[4]
- In immunocompromised hosts the immune response to Ixiaro is not well documented.
- Vaccination is recommended for residents of the Torres Strait Islands in Australia, as well as those traveling to the area for a cumulative total of 30 days during the wet season (December to May). Very few international tourists travel to the Torres Strait Islands, which are situated between the northern tip of Queensland and Papua New Guinea.

There are some JE vaccines available outside the USA in case travelers find themselves with last-minute plans while abroad, although use is generally discouraged without consultation. A live attenuated recombinant Vero cell vaccine (Imojev, Sanofi Aventis) is available in Australia and some countries in Asia, including Thailand, Malaysia, Hong Kong, Singapore, and the Philippines.[5] The vaccine is licensed for use in those aged 9 months. A single dose of 0.5 mL subcutaneously provides long-term protection in adults, but a booster is recommended for those aged 9 months to 18 years. Imojev is a live attenuated vaccine and therefore contraindicated in pregnant women, breast-feeding mothers, and immunosuppressed hosts. In Australia and New Zealand, Ixiaro is marketed as JEspect. In some countries a mouse brain-derived vaccine, with a poorly understood and worrisome safety profile, and other live attenuated vaccines, are also in use.[5] Given high risk of allergic responses with this product – including late onset of anaphylaxis – travelers are urged to seek travel advice in the US a few months prior to embarking on a trip to Asia to consider the safe and effective Ixiaro product. Hopefully, a coronavirus vaccine will also soon be available to facilitate all world travel once again!

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Epidemiology of Rabies and Current US Vaccine Guidelines

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ABSTRACT

Rabies is an acute encephalitis that is caused by rabies virus (RABV) infection, which belongs to the Rhabdoviridae family of viruses. It causes about 59,000 human deaths per year (although this number may be under-reported) and is generally fatal, once signs and symptoms begin to appear. Rabies is still very prevalent and under-reported, particularly in low to middle-income countries such as Asia and Africa, where there is lack of access to healthcare and domestic dogs are not widely vaccinated. Although not commonplace in the USA, rabies is mostly transmitted by wild animals such as bats, raccoons, skunks and foxes. Domesticated cats and dogs are also at risk of acquiring rabies, if they have not been vaccinated. Larger carnivores, such as coyotes, bobcats, mountain lions, wolves, bears, woodchucks, and beavers, should also be considered rabid (unless proven otherwise) if they are involved in an unprovoked attack on a person. The rabies vaccine can prevent 99% of deaths if administered promptly after exposure. There are two main vaccination strategies for rabies prevention: pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP). This article reviews background and epidemiology of rabies and current guidelines for rabies PrEP and PEP regimens for the United States.

KEYWORDS: rabies, animal bites, dogs, rabies vaccine, rabies immunoglobulin

BACKGROUND

Rabies is an acute progressive encephalitis caused by the rabies virus (RABV), a single stranded RNA virus that's part of the family Rhabdoviridae, genus Lyssavirus. The virus is most commonly transmitted through the saliva of a rabid animal. It can also be transmitted through exposure to urine, sweat, and nervous tissues. RABV is not considered to be a bloodborne pathogen. When a human/animal is bitten by a rabid animal, the virus travels from the bite wound into the peripheral nervous system and then makes its way to the brain where the virus replicates and then disseminates back into various tissues, including the salivary glands, where the transmission cycle repeats itself. Human-to-human transmission has never been confirmed except in extremely rare case reports of transmission from infected tissue/organ transplantation.[1] The incubation period on average lasts 1–3 months, but has been documented to range from weeks up to more than a year. Clinical rabies rarely occurs after one year from exposure.[2] Signs and symptoms include pain/paresthesias at the wound site, fever, paralysis, delirium, convulsions, and hydrophobia. Death is almost always imminent within 7–10 days once the infection clinically manifests itself. The rabies vaccine and rabies immunoglobulin (RIG) are very effective in preventing rabies if administered during the incubation period. Rabies vaccines activate the immune system to produce rabies virus neutralizing antibodies (VNAs). Detectable antibodies take about 7–10 days to develop and generally last for several years.

Louis Pasteur and Emile Roux developed and tested the first live attenuated injectable rabies vaccine in 1885. It was made from rabbit nerve tissue. Since 1984, the WHO has recommended discontinuation of production and use of nerve tissue vaccines and replacing them with modern, concentrated, purified cell culture and embryonated egg-based rabies vaccines (CCEEVs). Nerve tissue vaccines can cause severe adverse events and are not as effective. However, they are still being used in some developing countries. Since the 1960s, CCEEVs have been widely distributed and used in the U.S.2 There are two types of CCEEVs licensed for use in the U.S: human diploid cell vaccine (HDCV) and purified chick embryo cell vaccine (PCECV). Both are formulated for intramuscular (IM) administration and can be used for pre- or post-exposure prophylaxis.[3] Intradermal injections are sometimes used off license in the USA, but are not approved by the FDA.

There are two human RIG, HyperRabTM S/D and Imogam® Rabies-HT, licensed for use in the U.S. for PEP. They are IgG preparations made from human donor plasma and formulated for IM administration only.[3] RIG provides passive immunity that is intended to protect the victim until active immunity produced by the administered vaccine kicks in.

EPIDEMIOLOGY

Rabies causes about 59,000 deaths globally per year and associated loss of 3.7 million disease associated life years (DALYs). The majority of deaths occur in Asia and Africa.[2]

Children under 15 years account for approximately 40% of deaths.[5] Children are more susceptible because of their curious nature and their shorter stature, making them more likely to sustain a wound in a higher-risk anatomical location such as the head.[1] Transmission by unvaccinated domestic dogs is responsible for the majority of human rabies cases globally. Mass vaccination of domestic dogs has been an effective strategy at decreasing the prevalence of rabies in many countries in Africa, Asia, Europe and the Americas. Dog-mediated rabies has been eliminated from the U.S. (i.e. no cases of dog-mediated rabies in the last 2 years).[2] Rabies in the U.S. is rare and is now primarily transmitted through wild animal vectors such as bats, foxes, raccoons, and skunks. Since 1980, there has been an average of 2 deaths per year in the U.S. Between 2000 and 2007, 20 of 25 cases of human rabies reported in the United States were acquired domestically. Among those 20 cases, 17 were associated with bat rabies virus variants.[4] The rate of rabies exposures is about 16 to 200 per 100,000 travelers.[1] Approximately 16,000 to 39,000 patients are exposed to rabies and receive PEP annually in the U.S. Since routine use of cell culture vaccines and HRIG, no PEP failures have been reported in the United States.

PREEXPOSURE PROPHYLAXIS (PREP)

PrEP should be offered to high-risk populations, such as travelers who will spend a long time in a rabies endemic country, veterinarians and their staff, animal handlers, rabies researchers, certain laboratory workers, and those with frequent exposures to rabid animals (i.e. cavers, animal control officers).

In the United States, the Advisory Committee on Immunization Practices (ACIP) recommends a series of three 1-mL IM injections in the deltoid. Immunizations should be administered on days 0, 7, 21 or 28. If exposed to rabies, PrEP does not eliminate the need to seek out PEP; however, it reduces the number of vaccine injections post-exposure and eliminates the need for RIG. A few studies have demonstrated that a two-dose regimen given over the course of a week is just as effective as three doses, and more cost-effective.

Rabies occurs most often in resource limited settings. A clinical trial of 500 healthy volunteers showed that an intradermal 2-dose regimen given on days 0 and 7 did not elicit less of an immune response compared with a 3-dose regimen given over the course of a month.[6] The WHO recommends a 2-dose vaccination regimen in resource limited settings given on days 0 and 7 given either IM or ID.

SEROLOGIC TESTING

Rabies virus researchers or those who work in vaccine production are at highest risk for rabies and should get virus neutralizing antibody titer testing every 6 months. Those in the frequent exposure risk category (i.e. cavers, veterinarians, wildlife workers in areas where rabies is enzootic) require antibody titer testing every 2 years. If titers fall under the acceptable level of complete neutralization at a serum dilution of 1:5, a single IM booster vaccine should be administered. Routine antibody testing for travelers in the infrequent risk exposure category is not recommended.

POSTEXPOSURE PROPHYLAXIS (PEP)

All persons exposed to rabies should start by thoroughly washing and cleaning out the wound with soap and water or a virucidal agent. This should be followed immediately by passive rabies immunization with RIG in unvaccinated patients and vaccination with a cell culture rabies vaccine. HRIG is made from the plasma of hyperimmunized healthy volunteers and is not easily accessible in some resource poor settings. Equine rabies immunoglobulin may also be used as an alternative if HRIG is not available.

After a Rabies Workgroup met in 2008 to review current literature and expert opinion, the ACIP published revised guidelines in favor of reducing PEP vaccination from 5 doses to 4 doses.[5] Unvaccinated individuals should receive four 1-mL dose vaccines and RIG promptly after being exposed to the rabies virus. For adults and older children, the only acceptable area to administer the vaccine is in the deltoid area. In younger children, the outer thigh can be used as well. Vaccine should never be administered in the gluteal area because efficacy is decreased.

The first dose of the vaccine should be administered as soon as possible after the exposure on what is considered day 0. It can also be started weeks to months after exposure within the incubation period if signs and symptoms of rabies have not yet appeared. The next 3 doses should then be administered on days 3, 7, and 14 after the first vaccination. Serum antibody titer testing is not recommended for healthy patients as the vaccine has been shown to consistently produce adequate VNAs.

For immunosuppressed persons, rabies PEP should be administered by using the 5-dose vaccine regimen (ie, 1 dose of vaccine on days 0, 3, 7, 14, and 28). Immunosuppressed patients should undergo rabies serum antibody testing 1 to 2 weeks after the fifth dose of vaccine. The WHO specified minimum serum antibody concentration of 0.5 IU/mL is widely used as a measure of adequate seroconversion after vaccination.[2]

RIG should only be administered once on day 0 to exposed humans who have never previously received a complete vaccination regimen (pre- or post-exposure). If RIG administration is delayed, it can be administered at any time up to day 7.2 HRIG is intended to provide passive rabies VNAs while the active antibody production is occurring. After day 7, we presume that antibodies have already been produced from vaccine administration. The recommended dose for patients of all ages is 20 IU/kg of body weight. RIG should be

infiltrated around the wound(s) as much as possible and any remaining volume should be administered IM at an anatomical site distant from vaccine administration. RIG should be administered in a different syringe than the vaccine. No more than the recommended dose should be given because it may suppress active immunity production.[3]

Persons who have previously received complete vaccination regimens (pre-exposure or postexposure) with a rabies vaccine and have a documented rabies virus neutralizing antibody titer should receive only 2 vaccine injections 3 days apart (i.e. days 0 and 3). RIG should not be administered.

If an individual has a repeat exposure within 3 months, RIG and vaccine are not indicated. However, if the repeat exposure occurs >3 months, then the protocol for postexposure prophylaxis in a person who has been previously vaccinated should be followed (i.e. IM injection of vaccine on days 0 and 3).[2]

Minor deviations from the schedule by a few days are inconsequential. The schedule should be resumed with the same intervals between doses. For more substantial deviations from the schedule, antibody titers should be checked 1–2 weeks after the final dose of the vaccine is administered, as effects have not been properly studied.

Post exposure prophylaxis can be discontinued if the appropriate diagnostic laboratory testing (i.e., the direct fluorescent antibody test) concludes that the animal in question was not rabid.

ADVERSE EFFECTS AND SPECIAL CONSIDERATIONS

Serious hypersensitivity, neurological, and fatal adverse events following immunization are extremely rare. Considering the risk of death from rabies, there are no contraindications to rabies vaccination. Local symptoms of erythema, pain and swelling at the site of injection commonly occur. Mild systemic symptoms such as transient fever, headache, dizziness, nausea, and abdominal pain can present in about 5–15% of people after receiving the vaccine.[2] Prophylaxis should not be discontinued or interrupted because of minor or local adverse events.

Rabies vaccines and RIG should be administered normally to infants and children. Limited data suggests that rabies vaccines are safe in pregnancy and is not associated with abortion, premature births, or fetal abnormalities.[7]

Some studies suggest that antimalarial prophylaxis with chloroquine may blunt the immune response to rabies vaccine. According to the WHO, the effect of antimalarial agents on antibody production is unlikely to be clinically significant. They previously recommended IM over ID administration in persons taking antimalarial prophylaxis but removed this statement from their 2018 position paper.[2]

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