

Immunizations 2018 Part 1

Principles of Immunization, Influenza, Pneumococcal, Tetanus, Meningococcal, and Measles/Mumps/Rubella Vaccines

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Objectives:

Upon completion of this module, 70% of participants will rate their knowledge of the following as good or better:

1. Principles of immunization, including the risks associated with immunization.
2. Indications and contraindications for influenza vaccine.
3. Indications and contraindications for pneumococcal vaccine.
4. Indications and contraindications for tetanus vaccine.
5. Indications and contraindications for the measles/mumps/rubella vaccine.
6. Indications and contraindications for the meningococcal vaccine.

Cases

Case 1: Objective: Principles of immunization

Ophelia is a 27-year-old woman who is six months pregnant, and comes to clinic in November. Her favorite pastime is gardening and swimming. She mentions that she has been having trouble with her boyfriend. She asks you if it is safe for her to receive the flu shot. Her past medical history is otherwise unremarkable.

Which one of the following statements about vaccines is true?

- A. All vaccines are contraindicated in pregnant women, as in the case above.
- B. Killed virus vaccines induce longer lasting immunity than live-attenuated virus vaccines.
- C. Live attenuated virus vaccines in use include varicella vaccine and the measles/mumps/rubella (MMR) vaccine.
- D. Guillain-Barre syndrome may result from influenza vaccine, but is not described as a risk with other vaccines.
- E. Detectable antibodies after immunization are first noted six weeks following immunization.

Pop Up Answers

- A. Incorrect. Live, attenuated virus vaccines are contraindicated in pregnant women.
- B. Incorrect. Live attenuated virus vaccines produce longer-lasting immunity than killed virus vaccines.
- C. Correct! The intranasal influenza vaccine and the zoster vaccine are also live attenuated virus vaccines.
- D. Incorrect. Guillain-Barre syndrome has been described as a potential complication of other vaccines, including the tetanus booster and meningococcal vaccine.
- E. Incorrect. Detectable antibodies are first noted 7-10 days after immunization, and peak in two to six weeks.

Summary answer

The correct answer is **C: Live attenuated virus vaccines include varicella vaccine and the MMR vaccine (along with the intranasal influenza vaccine).**

Introduction

Immunization is the process of artificially inducing immunity in a host without exposure to natural infection, and, represents primary prevention of infectious diseases. Immunization relies on the creation of antibody to prevent infection. Immune memory (ability to mount a specific and rapid immune response upon a subsequent exposure to the targeted antigen) provides long-term protection against disease. Ultimately, the goal of vaccination is long-term disease protection (outcome change).

The topic of immunizations is covered in two modules focusing on some of the common vaccines and their adult dosing schedule. Module 1 covers principles of immunization, the influenza vaccines, tetanus vaccines, pneumococcal vaccine, and measles/mumps/rubella (MMR) vaccine. Immunizations for pediatric patients, as well as those planning international travel, are beyond the scope of this module. Travel immunization schedules can be found at:

<http://www.cdc.gov/travel/contentVaccinations.aspx>.

Active Immunization

Active immunization, or *vaccination*, is the induction of a protective host immune response in the recipient by administration of an antigenic substance, or *vaccine*. Because antibodies are produced by the host, the host's immune system must be functional. The primary antibody response to vaccination usually produces detectable circulating antibody (initially IgM) in 7-10 days, and peaks in 2-6 weeks.³ Active immunization may be achieved with live attenuated organisms, killed organisms (or its components), or manufactured products (e.g., recombinant DNA vaccines). The duration of antibody response to vaccine is variable, with some vaccines producing very long ranging responses (e.g., varicella-zoster, measles, and mumps) while others wane more quickly (e.g., pertussis).⁴ Live attenuated vaccines, which have been altered into non-pathogenic forms, produce a transient infection in the host, inducing a protective immune response and immunity that is typically long lasting. **Live vaccines, although productive of a long-lasting immune response, should generally be avoided in immunocompromised or pregnant patients.** Killed vaccines also induce a protective immune response, but often require repeat dosing to induce and maintain adequate immunity. Examples of vaccines are listed in Table 1.

Table 1: Common Vaccines

Vaccine	Manufacture
Influenza vaccine (injectable, trivalent)	Inactivated purified virus
Influenza vaccine (injectable, quadrivalent)	Inactivated purified virus
Influenza vaccine (injectable, trivalent)	Inactivated recombinant virus
Influenza vaccine (intranasal)	<i>Live attenuated virus</i>
Pneumococcal vaccine	PCV13: Conjugated protein PPSV 23: Polyvalent polysaccharide cell wall
Measles/Mumps/Rubella (MMR) vaccine	<i>Live attenuated virus</i>
diphtheria/Tetanus (Td) vaccine	Inactivated toxin (toxoid)
Diphtheria/Tetanus/acellular pertussis (Tdap) vaccine	Inactivated toxin (toxoid)
Meningococcal vaccine	Polyvalent polysaccharide cell wall or conjugate
Varicella vaccine	<i>Live attenuated virus</i>
Zoster vaccine	<i>Live attenuated virus</i>
Hepatitis A vaccine	Inactivated virus
Hepatitis B vaccine	Recombinant surface antigen proteins
Human papillomavirus vaccine	Recombinant surface antigen proteins

Passive Immunization

Passive immunization involves the administration of exogenously produced antibody. Typically human immunoglobulin obtained from plasma of blood donors is injected into the recipient. Passive immunization is used when immediate immunity is desirable (e.g., when an exposure is anticipated before vaccination can take effect, or when infection has already taken hold). Passive immunization is also used when the recipient is incapable of producing an adequate response to the vaccine, as in immunocompromised patients. The protection provided with passive immunization is short-lived, as the exogenous antibody is eventually cleared from circulation.

Risks of Vaccination

From the earliest days of Jenner and Pasteur, the public has expressed concern about the safety of vaccination. These concerns were muted in the era of polio vaccination, because the benefits of

receiving the vaccine were so clear. With the success of immunization, however, has come a loss of awareness of their benefits and a greater focus on their potential hazards. However, currently licensed vaccines have been shown repeatedly to be safe and effective. Two of the most commonly discussed areas of concern relate to the risk of Guillain-Barre syndrome with influenza vaccine, and the role of thimerosal (a preservative used in vaccines) in causing disease (especially autism).

Influenza Vaccine and Guillain-Barre Syndrome

Perhaps the most important adverse reaction to a vaccine was the development of Guillain-Barre syndrome (GBS) in a significant number of people who received the influenza vaccine in 1976 (the "swine flu" vaccine, not to be confused with the swine flu (H1N1) vaccine of 2009). The [majority of patients](#) who develop GBS associated with influenza vaccine do so in the second week following vaccination.⁵ This concern should be balanced with the fact that most cases of GBS are provoked by an acute infectious illness (such as influenza itself), rather than the vaccine. Analysis of all reported cases of GBS following influenza vaccine showed that the rate of GBS has decreased, especially after 1996.⁶

Influenza vaccine is not the only vaccine that has been linked to the development of GBS; tetanus toxoid, MMR, hepatitis B vaccine, meningococcal conjugate vaccine, smallpox, rabies and even BCG administration have been anecdotally linked to the development of GBS. Immunization after a neurologic illness should be delayed by a year to minimize the risk of development of GBS.⁷

Thimerosal, Mercury, and Allergic Reactions

Thimerosal is a mercury-containing organic compound that is added in small amounts to certain vaccines as a preservative, usually multi-dose vials. While the amount of mercury present in those vaccines that contain thimerosal is miniscule, [concern](#) has been raised about the possible role of this trace element in causing neurobehavioral disorders in children, notably autism. This reported association is based on the observation that increased rates of autism over the last few decades have paralleled the increased use of thimerosal-containing vaccines, and that some children with autism have been found to carry elevated levels of mercury. Two cohort studies performed by the

CDC, however, have failed to show an association between thimerosal and autism, and a population based [cohort](#) of children born in Denmark in the 1990s failed to demonstrate any causal relationship between thimerosal-containing vaccines and autism.⁸ Nonetheless, vaccine manufacturers removed thimerosal from most vaccines (with the exception of some influenza vaccines) and data from an autism registry indicate that the prevalence of autism in children did not decrease after this change.⁹ An influential study published in *The Lancet* in 1998 linking autism with the MMR vaccine has been retracted following evidence of scientific misconduct by the lead author. Yet controversy persists about whether exposure to thimerosal in childhood vaccines is responsible for the increased prevalence of autism.

Prior to immunization of any patient, you should consider the risks, benefits, and contraindications for that particular patient, as the risks and benefits vary between patients, particularly those with neurologic disease. That being said, there are several misconceptions about whether a vaccine should or should not be administered. In general, a vaccine is contraindicated in patients who have had a severe allergic reaction (i.e., anaphylaxis) following a previous dose of the same vaccine, or if the patient has a known severe allergic reaction to a vaccine component. Egg allergy, previously a contraindication to influenza vaccine, is now only a contraindication if eggs induce anaphylaxis. Individuals who get a rash with eggs may be safely administered injectable, inactivated influenza vaccine (the live-attenuated intranasal version should still be avoided in these patients). The recombinant influenza vaccine does not contain egg protein. Patients with moderate or severe acute illness should probably have vaccination delayed until the acute illness has resolved. However, mild illness (even with fever), is not a contraindication to receiving a vaccine, nor is current treatment with antibiotics a contraindication to receiving a vaccine (except for the live typhoid vaccine). These recommendations are reviewed in Table 2.

Table 2: Contraindications and Misconceptions About Vaccine Administration

Contraindications	Misconceptions
Absolute: • Serious allergic reaction (e.g., anaphylaxis) after a previous dose of the same vaccine • Serious allergic reaction (e.g., anaphylaxis) to a vaccine component Relative: • Moderate to severe acute illness, with or without fever • History of Guillain-Barre syndrome within 6 weeks of previous influenza vaccine	Contrary to misconception, vaccine administration is acceptable in the following clinical scenarios: • Mild acute illness, with or without fever • Mild to moderate local reaction or low-grade to moderate fever after previous dose • Current antimicrobial therapy • Convalescence from acute illness • Recent exposure to an infectious disease • History of penicillin allergy • History of other non-vaccine allergies • Relative with vaccine allergy • Receiving allergen immunotherapy Mild egg allergy (e.g., rash) is not a contraindication to injectable, inactivated influenza vaccine.

Case 2: Objective: Indications and contraindications for influenza vaccine

Rosencrantz and Guildenstern are 35-year-old men who come to see you in October for their annual checkup. They mention that they are planning an extended vacation to England, traveling by cruise ship. They are very excited and say, "We are just dying to go on this trip!" They are both allergic to eggs - Rosencrantz gets a rash and Guildenstern gets angioedema. Physical exam is unremarkable. After examining them, they ask you how to prevent getting sick this winter, and inquire about the influenza vaccine. Which one of the following statements is correct?

- A. Because of their young age, influenza vaccine is not medically indicated.
- B. You realize that the flu vaccine this year is not a 'good match' to the circulating virus, you advise them that they should not be vaccinated based on this information.
- C. The injectable, inactivated influenza vaccination should be given to Rosencrantz, but not to Guildenstern.
- D. Live-attenuated influenza virus vaccine is indicated in all adults regardless of age who are not immunocompromised.

Pop Up Answers

- A. Incorrect. Influenza vaccination is indicated for all adults.
- B. Incorrect. Although influenza vaccines are most effective when there is a good match between circulating viruses and the vaccine strains, protection may be substantial during years with a poor match.
- C. Correct! Mild egg allergy is not a contraindication to injectable, inactivated influenza vaccine, but angioedema is. Live-attenuated influenza vaccine (LAIV) remains contraindicated in those with any egg allergy.
- D. Incorrect. LAIV is indicated in healthy adults up to age 49.

Summary answer

The correct answer is **C: The injectable, inactivated influenza vaccination should be given to Rosencrantz, but not to Guildenstern.**

Influenza Vaccines

Influenza viruses (influenza A, influenza B, and influenza C) are in the family of viruses known as *Orthomyxoviridae*. Influenza A, which causes more severe disease than influenza B, is categorized based on two surface antigens: hemagglutinin (H) and neuraminidase (N). There are 16 known H subtypes and 9 known N subtypes of influenza A viruses. Many different combinations of H and N proteins are possible. Each combination represents a different subtype. The most common circulating strains of influenza A are H1N1, H3N2, and H1N2. It is these 3 subtypes that are commonly circulating among humans causing influenza A infections. Influenza B is not categorized into these subtypes. Influenza C does not cause clinically significant disease. Influenza virus characteristics are reviewed in Box 1 below.

Box 1: Influenza Virus Characteristics

- Single-stranded RNA virus
- *Orthomyxoviridae* family
- 3 types: A, B, C
 - Type A
 - Moderate to severe illness
 - Affects all age groups
 - Affects humans and other animals
 - Type B
 - Milder disease
 - Primarily affects children
 - Affects humans only
 - Type C
 - Rarely reported in humans
 - Not a cause of epidemics
- Subtypes of type A determined by hemagglutinin and neuraminidase

Influenza is a common cause of hospitalization, particularly in the elderly or the infirm. On average, there are 114,000 influenza-related excess hospitalizations annually, which are usually worse during epidemics by type A H3N2 viruses.³ Fatalities are not from influenza per se; rather, from pneumonia or exacerbation of cardiopulmonary conditions. The risk of influenza-related death increases with increasing age.¹⁰ As the US population ages, the impact of influenza on morbidity and mortality will increase.

Prevention of influenza, particularly among the elderly, is a stated national health priority. Prevention can be achieved through vaccination or chemoprophylaxis. Influenza vaccine is effective in healthy adults and results in 27% fewer lost work days due to febrile upper respiratory infections, 18%-37% fewer days of healthcare provider visits due to febrile illness and 41%-45% fewer days of antibiotic use.¹⁰ **Vaccination remains the preventive method of choice;** chemoprophylaxis is useful in specific clinical scenarios (discussed below). There is room for improvement in immunization rates; in the 2004-05 season 62.7% of those ages 65 and older were immunized.¹¹ October or November is the optimal time for flu vaccine, but the vaccine remains clinically useful in December, January and later. Flu season can begin as early as October and last as late as May.

Features of the Vaccine

The influenza vaccine is different every year. Infection data of influenza activity worldwide are analyzed in the spring, and an educated decision is made on which strains are likely to predominate in the coming winter. Antigenic variation in influenza viruses may result from antigenic drift (minor changes in either the hemagglutinin and/or neuraminidase structures) or antigenic shift (i.e., a major change, via replacement of the hemagglutinin and/or neuraminidase structures). Antigenic drift may occur with influenza A or influenza B. Antigenic shift only occurs with influenza A. Antigenic shift is associated with [more severe outbreaks](#) of influenza, and was seen with the 2009 H1N1 flu.¹² The differences between antigenic drift and shift are summarized in Box 2 below.

Box 2: Antigenic drift vs. antigenic shift

- **Antigenic Drift**
 - Minor change, same subtype
 - Caused by point mutations in gene
 - May result in epidemic
- **Antigenic Shift**
 - Major change, new subtype
 - Caused by exchange of gene segments
 - May result in pandemic

A characteristic unique to influenza vaccine is the possibility of miscalculation of the viral strains expected to predominate in the coming influenza season. **Even when the predominant strain of influenza is miscalculated, the vaccine offers protection.** Both the inactivated vaccine and the live-attenuated vaccine are efficacious in preventing laboratory-confirmed symptomatic illnesses from influenza in healthy adults.¹³ For the U.S. [2014-15 influenza season](#) there was a mismatch in the H3N2 strain of the vaccine and yet there was still a 23% reduced risk of medical visits associated with seasonal influenza illness (range of 10%-60% visit reduction attributed to vaccination since 2005). However, the 2014-15 flu-associated hospitalization rate among people 65 and older was the highest rate recorded since the CDC began tracking the data in 2005.

Inactivated influenza vaccine (IIV)

Three influenza strains (trivalent) are typically combined in a vaccine; two strains of influenza A (one H1N1 virus and one H3N2 virus), and one strain of influenza B.³ For the newer quadrivalent influenza vaccines, four strains have been combined; 2 strains of influenza A and 2 strains of influenza B. The viruses are grown on embryonic hen's eggs, and are then inactivated and purified. The purification process is unable to remove all egg protein, so patients with a history of severe egg allergy (e.g., anaphylaxis) should not receive the vaccine. The IIV vaccine may be used in those with mild egg allergy (e.g., rash), and is administered normally.¹⁶

The inactivated influenza vaccine is completely inactivated, and does not cause influenza. Thimerosal is used as a preservative for some formulations of influenza vaccine (e.g., multidose vials), although thimerosal-free influenza vaccine is available in single-dose vials.

A higher dose formulation of an inactivated seasonal influenza vaccine may be used in people age 65 years and older. This high dose formulation contains four times the amount of influenza antigen compared to other inactivated seasonal influenza vaccines, and does result in higher antibody levels (as well as higher rates of local reactions).¹⁷ A retrospective cohort study of US Medicare beneficiaries showed that high-dose IIV was significantly more effective than standard-dose IIV in preventing influenza-related medical encounters including a significant reduction in influenza-related hospital admissions compared to standard-dose IIV in people ≥ 65 years of age.¹⁹ When considering total healthcare expenditures, high-dose IIV is less costly compared to the standard-dose IIV, given the reduction in the rates of influenza-related hospital admissions.¹⁷

Live attenuated influenza vaccine (LAIV)

An intranasal live attenuated influenza vaccine (LAIV) was made available in 2003. Like trivalent IIV, it is composed of two influenza A virus strains (one H1N1 and one H3N2 strain), and one influenza B virus strain.

Unfortunately, data from the 2014 and 2016 flu season showed that the live-attenuated influenza vaccine was not very effective in protecting against influenza. Additionally, the revised recommendations for the use of influenza vaccine among adults with egg allergy include alternatives to LAIV. As a result, ACIP recommends against using the live-attenuated influenza vaccine for the 2017 flu season.¹⁸

Recombinant influenza vaccine (RIV)

A recombinant flu vaccine has been developed and is available for people aged 18-49 years old. This trivalent influenza vaccine contains 2 influenza A strains (H1N1 and H3N2), and one influenza virus B strain. It is made using an insect virus (baculovirus) expression system and recombinant DNA technology. Unlike other flu vaccines, the recombinant flu vaccine does not use the influenza virus or eggs in its production and can be used in people with egg allergy of any severity. A comparison of IIV, LAIV, and RIV is provided below.

Table 3: Comparison of Inactivated Influenza Vaccine (IIV); Trivalent Live, Attenuated Influenza Vaccine (LAIV); Recombinant Influenza Vaccine (RIV)¹⁸

	IIV	LAIV	RIV
Influenza strains	Annually recommended strains of influenza viruses	Same as IIV	Same as IIV
Manufacture	Virus strains grown in eggs	Same as IIV	Insect virus and recombinant DNA
Frequency of administration	Annually	Annually	Annually
Efficacy	When vaccine and circulating viruses are antigenically similar, vaccine prevents influenza 70 to 90% among healthy adults <65 years of age	Recent data suggests decreased efficacy of LAIV, ACIP now recommending against its use for 2017-8 flu season	44.6% effective against all circulating influenza strains, not just strains matching those included in the vaccine
Virus state	Killed (inactivated) viruses	Live, attenuated viruses still capable of replication	Recombinant
Route of administration	Intramuscularly by injection	Intranasally by sprayer	Intramuscularly by injection
Approved age and risk groups	Approved for use among persons ≥6 months of age, including both those who are healthy and those with chronic medical conditions	Approved for use only among healthy persons aged 2-49 years	18-49 years
Use in egg allergy?	Acceptable for use in those with mild egg allergy (e.g., rash)	Contraindicated in all patients.	No contraindications.

Efficacy Data

When there is a high degree of similarity between the vaccine and the dominant influenza strain causing illness in a given year, influenza vaccine [prevents](#) influenza in 70-90% of healthy adults <65 years.²¹ Unfortunately, in the group most in need of effective vaccine (i.e., those 65 and over), vaccine [efficacy is lower](#).²² However, even when not preventing illness, influenza vaccine has been [proven](#) effective in attenuating illness from influenza in healthy adults and in the [elderly](#).²³ Influenza vaccine [reduces](#) the risk of hospitalization, pneumonia, and death in the elderly²¹ and in persons with [high risk medical conditions](#).²⁵ In addition to the annual benefit from influenza vaccination, there may be cumulative benefit from annual influenza vaccination in the elderly. One [study](#) showed that elderly individuals vaccinated more than one year in a row had a 15% reduction in mortality risk as compared to those vaccinated for the first time.²⁶

Indications

All adults are recommended to receive annual influenza vaccination. The indications for immunization with IIV differ from indications for immunization with LAIV. IIV is recommended in all adults, as well as pregnant women and people any age with chronic medical conditions such as heart disease, lung disease, diabetes, or immunosuppression, or who live with or care for those at high risk for complications from the flu.

LAIV may be administered to healthy, non-pregnant persons aged 19-49 years for whom the vaccine is not contraindicated, including healthcare workers and other close contacts of high-risk persons. Healthcare workers should avoid contact with immunocompromised patients for 7 days following LAIV.²⁷ If a person sneezes after receiving LAIV, the dose should not be repeated. No data exist regarding concomitant use of nasal corticosteroids or other intranasal medications when receiving LAIV.²⁸ RIV can be administered to adults aged 19-49.

Case 3: Objective: Contraindications to influenza vaccine and chemoprophylaxis

Your next patient, Polonius, is a judge, who is a pompous, scheming old man. He has questions regarding himself and his 2 children, Laertes and Ophelia, regarding protection against influenza. He has a severe egg allergy, and wonders about other approaches to preventing influenza. He also wonders which of the following is true?

- A. Having a fever is a contraindication to receiving LAIV, but not IIV.
- B. Egg allergy is a contraindication to receiving IIV, but not LAIV.
- C. Chemoprophylaxis to prevent influenza is inferior to vaccination at reducing influenza morbidity and mortality among a community.
- D. If chemoprophylaxis is to be used in an individual in conjunction with influenza vaccination, LAIV, not IIV, should be used to vaccinate the individual.

Pop up answers

- A. Incorrect. Fever is not a contraindication to either LAIV or IIV.
- B. Incorrect. Egg allergy is a contraindication to LAIV. IIV may be used in individuals with mild egg allergy (e.g., rash), but not those with severe egg allergy.
- C. Correct. Chemoprophylaxis is inferior to influenza vaccination. Chemoprophylaxis will be ineffective for drug-resistant strains of influenza and does not increase herd immunity among a population.
- D. Incorrect. If chemoprophylaxis and vaccination are used concurrently (e.g., a high-risk patient just exposed to influenza), IIV should be used for vaccination. With LAIV, chemoprophylaxis will prevent replication of the live, attenuated influenza virus, thereby limiting the immune stimulus.

Summary answer

The correct answer is **C: Chemoprophylaxis to prevent influenza is inferior to vaccination at reducing influenza morbidity and mortality among a community.**

Having learned about when to use the influenza vaccine and in whom, we now review when not to use the vaccine and alternatives to influenza prevention.

Contraindications

As with all medications, neither IIV nor LAIV should be given to individuals with a known allergy to the vaccine. Both IIV and LAIV are contaminated with egg protein, and are contraindicated in those with egg allergy. While a mild febrile illness is not a contraindication to either vaccine, moderate to severe illness should prompt postponement of immunization.

The contraindications for LAIV are more expansive than those for IIV (see table below). All chronic medical conditions (e.g., heart disease, lung disease, hemoglobinopathies, diabetes, renal dysfunction, and immunodeficiency) are contraindications to LAIV. A history of Guillain-Barre syndrome is a contraindication to LAIV. Pregnancy is also a contraindication to LAIV. LAIV should not be administered to a patient who has significant nasal congestion. LAIV should not be administered in conjunction with anti-influenza antiviral medications.

Table 4: Contraindications to Influenza Vaccine

Vaccine	Contraindications
Inactivated Influenza Vaccine (IIV)	• Severe egg allergy (e.g., angioedema; anaphylaxis) • Severe allergy to other vaccine components
Live Attenuated Influenza Vaccine (LAIV)	• People with a history of hypersensitivity, including anaphylaxis, to any of the components of LAIV or to eggs • People aged < 2 years or those aged >49 years • People with any of the underlying medical conditions ○ Heart Disease (except hypertension) ○ Lung disease (including asthma or reactive airways disease) ○ DM, or other metabolic disease ○ Hepatic diseases ○ Renal dysfunction ○ Hemoglobinopathies ○ Immunosuppression ○ Conditions with compromised respiratory function or difficulties handling secretions (cognitive dysfunctions, seizure disorder, spinal cord injury) • Children or adolescents receiving aspirin or other salicylates • Individuals with asthma and children < 5 years with a history of recurrent wheezing • People with a history of GBS • Women who are pregnant
Recombinant Influenza Vaccine (RIV)	• Severe allergy to any vaccine component • Age <18 years

Adverse Reactions

Patients may experience upper respiratory tract infection symptoms after receiving the vaccination, but this is probably because the flu vaccine is administered in the fall or early winter-- a time of high incidence of unrelated upper respiratory tract infections. Actual adverse effects of the IIV vaccine are generally limited to soreness at the injection site, which may occur in as many as 70% of recipients. Systemic reactions occur with the same frequency as placebo. Even less common are hypersensitivity reactions, which occur only in those with egg allergy.

Rhinorrhea, sore throat, and headache are the most common side effects seen with LAIV. A review of adverse events from the LAIV found 460 adverse events out of 2.5 million doses.^{28, 29} Of those adverse events, the most common was flu-like illness, followed by allergic reactions (although anaphylaxis was rare). Secondary transmission comprised 4.8% of adverse reactions; while asthma exacerbations comprised 2.6% (note asthma is a contraindication for receiving LAIV).

Chemoprophylaxis

There are clinical scenarios in which immunization may not be desirable, yet prevention of influenza remains an acute health care need. As immunization takes 7-10 days to induce a protective response, an unimmunized patient exposed to influenza may require chemoprophylaxis to prevent influenza. Table 5 lists the people who may be considered for chemoprophylaxis.

Table 5: Chemoprophylaxis

Potential candidates	Whom not to treat chemoprophylactically
• Persons at high risk for complications of influenza • Health care workers and emergency medical personnel • Pregnant woman	• Groups of healthy children or adults based on potential community, workplace, school, or other exposure • If >48 hours have elapsed since last close* contact • Those immunized with LAIV

*Close contact, defined by possible modes of transmission: droplet exposure of mucosal surfaces to respiratory secretions from coughing or sneezing, contact (hands) with an infectious patient, small particle aerosols in the vicinity of an infectious person.

Four licensed influenza antiviral agents are available in the United States and represent candidates for chemoprophylaxis: the adamantanes (amantadine and rimantadine, effective against influenza A), and the neuraminidase inhibitors (oseltamivir and zanamivir, effective against influenza A and influenza B). Because a high proportion of circulating influenza viruses in the US are resistant to the adamantanes, the value of these drugs for chemoprophylaxis is limited, and they should probably not be used for this purpose. Oseltamivir and zanamivir are better choices, but won't be effective when antiviral-resistant strains of influenza predominate.³⁰

Use of oseltamivir and zanamivir was associated with a 19% [reduction in mortality](#) among hospitalized patients during the 2009 H1N1 influenza pandemic. Since influenza vaccine, like all vaccines, takes 7-10 days to result in detectable antibody production, the scenario may arise in which chemoprophylaxis is given to a just-vaccinated person to protect that individual pending an immune response. An example would be a high-risk person exposed to influenza who then decides to undergo immunization but needs chemoprophylaxis to protect against the exposure. Chemoprophylaxis should not be used in individuals immunized with LAIV, as the drug will prevent the viral replication of the attenuated virus. Therefore, if both immunization and chemoprophylaxis are to be given concurrently, IIV (and not LAIV) should be used in conjunction with chemoprophylaxis.

Treatment of influenza is discussed in the upper respiratory tract infection module.

Case 4: Objective: Indications and contraindications for PPSV23 pneumococcal vaccine

Your next patient is Claudius King, a 73-year-old male with diabetes and hypertension, both well controlled. He was formerly an ear drop chemist, who has inherited the family business, and has been having trouble with his new stepson. You note from the chart that he received a pneumococcal vaccination with PPSV23 seven years ago.

Which ONE of the following statements about PPSV23 pneumococcal vaccine is true?

- A. PPSV23 is given every 5 years; therefore he needs a booster.
- B. In patients over age 65, PPSV23 should be repeated 10 years after the initial administration; Mr. King will be due for a repeat dose in 3 years.
- C. Because Mr. King received PPSV23 after the age of 65, revaccination with PPSV23 is not medically indicated.
- D. Patients felt to be at high risk for pneumococcal infection should receive a repeat dose of PPSV23 every five years following vaccination.

Pop Up Answers

- A. Incorrect. Repeat vaccination is indicated for certain high-risk subgroups. Otherwise it is a one-time only vaccine at the age of 65 years.
- B. Incorrect. Repeat vaccination is indicated for certain high-risk subgroups. Otherwise it is a one-time only vaccine at the age of 65 years.
- C. Correct. Revaccination is indicated in certain high-risk populations if the primary vaccine is given when the patient is <65 years old. If an individual is vaccinated at age 65 or older, revaccination is not medically indicated, even in high-risk populations.
- D. Incorrect. Only a single revaccination is indicated for patients at high risk, provided the initial vaccine was given before the patient's 65th birthday. High-risk patients are also revaccinated at age 65, or 5 years after their most recent vaccination (whichever comes later).

Summary answer

The correct answer is **C: Because Mr. King received PPSV23 pneumococcal vaccine after the age of 65, revaccination with PPSV23 is not medically indicated.**

Pneumococcal Vaccine

Infection with *Streptococcus pneumoniae*, a Gram positive coccus encapsulated with a polysaccharide coat, causes 40,000 deaths annually, making pneumococcal vaccine among the best candidates (along with influenza vaccine) for reducing mortality of all vaccines in use.³ *Streptococcus pneumoniae* is the leading cause of pneumonia in this country (500,000 cases) and

also causes otitis media, sinusitis, as well as bacteremia and meningitis (the latter two, along with pneumonia, contribute significantly to the mortality associated with pneumococcal infection). The increasing prevalence of antibiotic-resistant *Streptococcus pneumoniae* increases the value of the pneumococcal vaccine. Rates of pneumococcal vaccination among those at risk remain low.

Some populations are more at risk for serious pneumococcal infection than others. Those patients who do not have a functioning spleen (which plays a vital role in clearance of encapsulated organisms), are at risk for fulminant pneumococcal infection. Patients who are immunocompromised for other reasons (e.g., chemotherapy, HIV) are also at increased risk for serious disease. As we saw with influenza, those aged 65 and older are at increased risk as well. Additionally, cigarette smoking has been [shown](#) to be a risk factor for the development of pneumococcal disease.³²

The Pneumococcal Vaccines

The polysaccharide coat of pneumococcus determines its virulence. These polysaccharide coats are antigenically distinct, resulting in different serotypes of pneumococcus. Serotypes have been numbered from 1-90. Since the first pneumococci described were those that cause significant human disease, the most virulent strains typically have lower numbers.³

It is against antigenic determinants in the polysaccharide coat that the pneumococcal vaccine is targeted. The most widely-used adult pneumococcal vaccine consists of capsular polysaccharides from the 23 serotypes of pneumococcus that most commonly cause disease in humans, and is known as the pneumococcal polysaccharide vaccine, or PPSV23.³ A formulation of the 13 most virulent strains of pneumococcus has been developed, and is known as the pneumococcal conjugate vaccine, or PCV13. PCV13 [may be more immunogenic](#) than PPSV23.³² Because of this, PCV13 is now the recommended initial vaccine. Adults should receive 1 dose of PCV13 and 1, 2, or 3 doses (depending on indication) of PPSV23.

Thimerosal is used as a preservative in most formulations. Because the pneumococcal vaccine is polysaccharide based, it evokes a T-cell independent response. Therefore, immunity tends to wane with time, and anamnestic responses [do not occur](#) upon rechallenge with the antigen.

Efficacy Data

The efficacy of the vaccine in its protection against pneumonia and bacteremia remains debated in the literature. Some [studies](#) have demonstrated that the pneumococcal vaccine does not work in high-risk individuals, the population that would benefit the most from an effective vaccine.³³ It may be that the same mechanism that puts individuals at risk for developing infection with encapsulated organisms prevents them from responding to the polysaccharide vaccine. Even a [study](#) of healthy adults (i.e., those most likely to respond to the vaccine) failed to demonstrate a reduction in the risk of development of pneumococcal pneumonia.³⁴ However, there have been other [studies](#) demonstrating the clinical utility of the pneumococcal vaccine, and doubts about its efficacy should not dissuade patients or physicians from considering the pneumococcal vaccine in the appropriate clinical setting.^{35, 36}

Indications

The CDC lists the following groups (Table 6) as candidates for vaccination.^{37, 38}

Table 6: Indications for Pneumococcal Vaccine

Age Group	Vaccine Candidates
Adults aged 18-64	Any of the following: • Heart disease • Lung disease (including asthma) • Liver disease • Alcoholism • Diabetes • Renal dysfunction (including nephrotic syndrome) • CSF leaks • Asplenia (functional or anatomic) • Sickle Cell Disease • Immunocompromised (e.g., malignancy, chemotherapy, HIV, organ transplant) • Long-term corticosteroid use • Cochlear implant recipients • Residents of long-term care facilities • Cigarette smokers
Adults aged 65 or older	• All individuals

Pneumococcal vaccine can be considered in Alaska natives and American Indians who are living in areas in which the risk of invasive pneumococcal disease is increased.

Revaccination

For most persons for whom pneumococcal vaccine is indicated, the ACIP does not recommend routine revaccination. However, one-time revaccination 5 years after the first dose of PPSV23 is recommended for persons aged 19 through 64 years with functional or anatomic asplenia (e.g., sickle cell disease or splenectomy), or immunocompromising conditions (see Box 3).^{37,38}

Individuals who received 1 or 2 doses of PPSV23 before age 65 years for any indication should receive another dose of the vaccine at age 65 years (or later) if at least 5 years have passed since their previous dose. No further doses of PPSV23 are needed for persons vaccinated with PPSV23 at or after age 65 years. High-risk conditions for which revaccination (if age<65) is recommended are listed in Box 3.

Box 3: Indications for Pneumococcal Revaccination

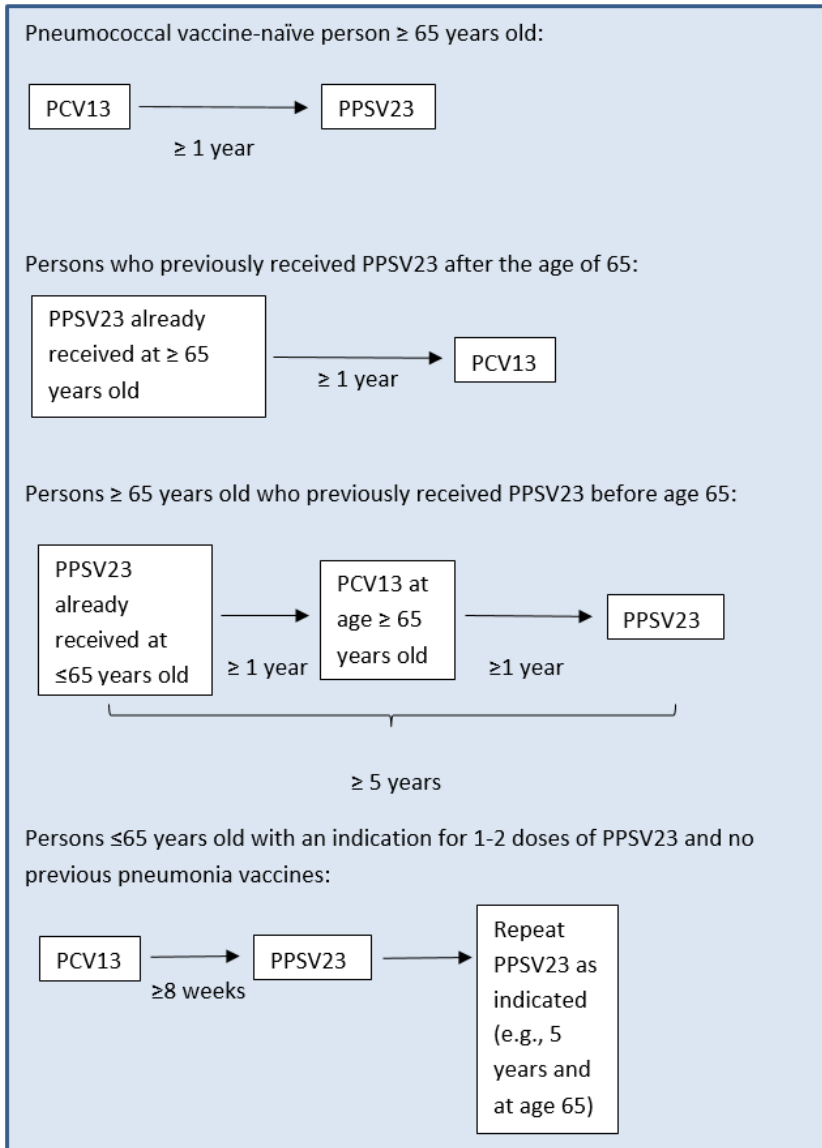
- Functional or anatomic asplenia (e.g., sickle cell disease or splenectomy)
- HIV
- Malignancy
- Chronic kidney disease
- Organ transplant
- Nephrotic syndrome
- Chemotherapy
- Corticosteroid administration

PCV13

As mentioned above, PCV13 was released in 2012, targeting the 13 most pathogenic pneumococcal serotypes. It appears to be more immunogenic than PPSV23. For this reason, PCV13 should be the initial pneumococcal vaccine given to adults aged 65 and older. The ACIP simplified guidelines for the time intervals for PCV13 and PPSV23 vaccines and now recommend the same time intervals regardless of the order of the vaccines.³⁷ Immunocompetent individuals aged 65 years and older who have not received any pneumococcal vaccine should be given PCV13 first, followed by a dose of PPSV23 after at least 1 year. Individuals who already received PPSV23

when they were aged 65 years or older should be given PCV13 at least 1 year following the PPSV23 dose. Individuals aged 65 and older who received PPSV23 vaccine before they were 65 should be given PCV13, followed by PPSV23 at least 1 year later. Recommended intervals between PCV13 and PPSV23 for individuals with medical indications to receive both vaccines remain unchanged. PPSV23 is recommended to be given ≥ 8 weeks after PCV13 for individuals with certain underlying medical conditions (including adults aged ≥ 65 years with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants). The currently recommended 8-week interval minimizes the risk window for invasive pneumococcal disease caused by serotypes unique to PPSV23 in these highly vulnerable people. High-risk individuals younger than 65 years old, who have indications for pneumococcal revaccination, should receive PCV13 followed by PPSV23 8 weeks later and again in 5 years. Those high-risk patients who have already received PPSV23 should be vaccinated with PCV13 no sooner than 1 year after their PPSV23 dose. Revaccination should proceed according their PPSV23 dose (see figure below). If a dose of PPSV23 is inadvertently given earlier than the recommended interval, the dose need not be repeated.

Pneumococcal Vaccine Sequence and Intervals



Adapted from MMWR³⁷

Contraindications

The only contraindication to pneumococcal vaccination is known allergy to the vaccine itself or any of its components. As with the influenza vaccine, moderate or severe acute illness should prompt delay until the patient has recovered. As this is not a live attenuated virus vaccine, it is not contraindicated in pregnant women. Pneumococcal vaccine may be co-administered with other vaccines, with the notable exception of the zoster vaccine. Co-administration of the pneumococcal vaccine and the zoster vaccine results in decreased immunogenicity of zoster vaccine.

Adverse Reactions

The pneumococcal vaccine is well tolerated. Adverse reactions are rare.

Recap

Table 7 lists the indications and contraindications for pneumococcal vaccine.

Table 7: Pneumococcal Vaccine Indications and Contraindications

Indications	Contraindications
- Adults 65 years of age or older. - Persons of any age with significant chronic cardiovascular or pulmonary disorders (including asthma) - Persons of any age with splenic dysfunction asplenia, Hodgkin's Disease, multiple myeloma, cirrhosis, alcoholism, renal failure, CSF leaks, immunosuppressive conditions - Individuals who smoke	- Allergy to vaccine components, anaphylactic reaction to the vaccine or a constituent of the vaccine. - Acute, moderate or severe illnesses with or without fever

Case 5: Objective: Indications and contraindications for tetanus vaccination

Your next patient is Hamlet, a healthy, active 32-year-old man, who is new to your clinic. His past medical history is notable only for insomnia, after his father's demise. He complains that his mother and girlfriend don't understand him. He is otherwise in remarkably good health, and doesn't smoke. Hamlet has remained active with his friends, and is involved in sports such as fencing. On physical exam, blood pressure is 132/72; a puncture wound is present on his right shoulder, which he states he received yesterday during a fencing duel. Because of this injury, you suggest that he get a tetanus booster. He states that he received one eight years ago, and doesn't see why he needs one now.

Which ONE of the following statements is correct?

- A. The patient is correct; he is protected from development of tetanus, and no further treatment is indicated.
- B. He should be reimmunized with a tetanus booster; wounds that occur more than five years after the most recent tetanus immunization should prompt reimmunization.
- C. It is too late to immunize the patient for the wound received yesterday; he should be given tetanus immune globulin.
- D. Had he never been immunized, a tetanus booster should be administered today and again in two weeks.

Pop Up Answers

- A. Incorrect. Fresh wounds should prompt a tetanus booster if their last booster was greater than five years ago.
- B. Correct. Wounds that occur more than five years after the most recent tetanus immunization should prompt reimmunization. If the person receiving immunization has not received the Tdap, then this formulation should be used.
- C. Incorrect. He will still benefit from updating his tetanus immunity.
- D. Incorrect. Tetanus immune globulin should be administered to individuals who have a puncture wound and no history of tetanus immunization.

Summary answer

The correct answer is **B: He should be reimmunized with tetanus booster; wounds that occur more than five years after the most recent tetanus immunization should prompt reimmunization.**

Tetanus immunization

Tetanus is a clinical syndrome involving the nervous system, which results in severe, painful muscle spasm. The manifestations of tetanus are due to production of the toxin tetanospasmin, following infection with *Clostridium tetani* (an anaerobic gram positive bacillus). Tetanospasmin is primarily a neurotoxin that prevents inhibiting signals between the nerve and muscle, leading to muscle spasm and muscle rigidity. The case fatality rate is 25%, and many patients require mechanical ventilation to support respiration. The diagnosis is a clinical one, and is most often confused with strychnine poisoning and occasionally with a dystonic reaction.

Clostridial spores, which are exceptionally stable, are typically inoculated during injury, and are more likely if the injury is contaminated with soil, feces, or saliva (Table 8). [Puncture wounds](#) (including needle injuries in injection drug users³⁹), crush injuries, and frostbite are among the high-risk injuries leading to clostridial infection. Once infection has been established, production of the exotoxin tetanospasmin occurs.

Table 8: Wounds for Which Tetanus Prophylaxis is Recommended

Wound type
• Contaminated wounds (e.g., dirt, feces, saliva) • Puncture wounds • Avulsions • Missile wounds • Crush injuries • Burns • Frostbite

Although tetanus is a rare disease (the U.S. incidence is 0.02/100,000 per year), it carries a high mortality and is preventable. Most cases occur in people 60 or older, usually after an acute injury. The injury may be as subtle as a prick from a thorn. Protective immunity is provided by the presence of neutralizing antibodies against the tetanus toxin *tetanospasmin*. Such immunity is inadequate among older adults, at [less than 28%](#) for those over 70.⁴⁰ This is in marked contrast to the prevalence of protective immunity among children, who have a >96% vaccination rate by school entry. As such, booster doses are recommended (intervals of revaccination are discussed below).

Features of the Vaccine

While many vaccines protect the host against infection by an infectious agent, some immunizations provoke immunity against a toxin produced by an infectious agent. Such is the case with tetanus. Tetanus toxoid is an inactivated formulation of tetanus toxin, and is given in series to develop immunogenicity. Most of the US population is immunized in childhood. Tetanus toxoid is usually given in combination with diphtheria toxoid (Td) to ensure continued immunity to diphtheria. The isolated tetanus toxoid vaccine should be used only when Td is unavailable. (The abbreviation for the vaccine, Td, indicates that a low dose of diphtheria toxoid is used, in contrast to TD, which has a higher dose of diphtheria toxoid. Td is favored over TD in adults because the high dose of diphtheria toxoid found in TD is more likely to cause side effects).

A formulation of the tetanus toxoid vaccine, [Tdap](#), contains diphtheria toxoid as well as an acellular pertussis vaccine. This formulation contains a full concentration of tetanus and lower concentrations of both diphtheria and pertussis, and was developed in response to a resurgence of pertussis. A single dose of Tdap is recommended for all adults regardless of age, replacing a planned vaccination with Td. With a goal of reducing the burden of pertussis in infants, Tdap is also recommended for all pregnant women with each pregnancy. Tdap can be given at any point during pregnancy but ACIP recommends administration during the third trimester in an effort to boost antibodies just before birth. Close contacts of infants aged less than 12 months, and all healthcare personnel with direct patient contact (if they have not previously received Tdap, regardless of how recent their last Td was) should also receive Tdap. Once given, future tetanus boosters should be given using the standard Td formulation.

Efficacy

The tetanus vaccine, which has been studied for efficacy in children, is among the most effective vaccines available, and is very immunogenic.³ Ninety-five percent of children immunized develop protective antibodies.³

Indications and Revaccination

Recommendations for tetanus vaccination in adults include administration of the vaccine at 10-year intervals, following the primary series given in infancy.³ Vaccine is also given after a tetanus-prone wound if more than 5 years have elapsed since the last booster. Pregnant patients should receive Tdap. Tetanus vaccine may be given in combination with other vaccines.

Tetanus immune globulin is prepared from human plasma prescreened for high levels of tetanus antibody. Tetanus immune globulin is used for passive immunization of those who have not received their primary series (or those with humoral immunodeficiency), who present with an injury that places them at risk for tetanus. Tetanus immune globulin may also be used in individuals who have a severe hypersensitivity reaction to tetanus toxoid and in the management of symptomatic tetanus as it shortens the course of disease.

If an adult presents with no history of ever having been immunized against tetanus, a primary series of immunization is recommended (you may consider this in recent immigrants, for example). Three doses are required to complete a primary series:

- Dose 1: Time zero
- Dose 2: 4 weeks later
- Dose 3: 6-12 months after dose 2

Td is used for two of the doses, and Tdap is used for one when administering the primary vaccination series.

Contraindications

Due to the immunogenicity of tetanus toxoid, recent immunization with tetanus vaccine is the most significant contraindication to tetanus toxoid (an Arthus-like reaction may develop). Past tetanus toxoid immunization resulting in adverse reactions would also be considered a contraindication.

Adverse Reactions

Tetanus toxoid is generally well tolerated, but may cause fever. Guillain-Barre syndrome has been described as a rare adverse reaction, as has brachial neuritis.

Indications for tetanus vaccination are reviewed in Table 9.

Table 9: Td/Tdap Vaccination Schedules

Primary Immunization Schedule	Td schedule	Tdap Schedule
Dose #1: Time zero Dose #2: 4 weeks later Dose #3: 6-12 months after dose #2 (One of three doses should be Tdap)	• Revaccinate every 10 years • Revaccinate now if at risk wound and >5 years since last vaccination	• Replace Td dose with Tdap once if revaccination with tetanus is otherwise indicated, regardless of age • All pregnant women, preferably in third trimester • If known exposure to infant planned, consider Tdap regardless of interval since last Td

Case 6: Objective: indications and contraindications for meningococcal vaccine

Fortinbras, a college freshman who lives at home, is planning a trip to Denmark after the untimely demise of his father. His past medical history is unremarkable except for a traumatic event early in his life that resulted in the removal of his spleen; he takes no medications. Other than issues with anger management, he is very healthy. Which of the following concerning the meningococcal vaccination are true for him?

- A. All college freshmen should receive the meningococcal vaccine.

- B. By receiving the meningococcal vaccine, Fortinbras will be protected against all major subtypes of meningococcus found in the US.
- C. Given his history of traumatic asplenia, Fortinbras should receive the meningococcal vaccine.
- D. Travel to Europe is an indication for meningococcal vaccine.

Pop Up answers

- A. Incorrect. The specific indication for meningococcal vaccine is college freshmen living in a dormitory.
- B. Incorrect. Serogroup B, which accounts for about a third of invasive disease, is not included in the vaccine. Work is underway to develop a vaccine for serogroup B
- C. Correct. Asplenia is among the indications for meningococcal vaccination.
- D. Incorrect. A person who travels to or resides in countries in which meningococcal disease is hyperendemic or epidemic (e.g., the 'meningitis belt' of Sub-Saharan Africa) should receive the meningococcal vaccine.

Summary answer

The correct answer is **C. Given his history of traumatic asplenia, Fortinbras should receive the meningococcal vaccine.**

This section reviews the indications and contraindications for meningococcal immunization.⁴¹

Introduction

Neisseria meningitidis is an encapsulated Gram negative diplococcus that most commonly causes any of three types of disease: meningitis (50% of cases); blood stream infection (30% of cases), and pneumonia (10% of cases). There are at least 13 serogroups based on characteristics of the polysaccharide capsule. The most invasive disease is caused by serogroups A, B, C, Y, and W-135. Humans are the only reservoir, and nasal carriage is seen in up to 10% of the population. Every year, there are between 1000-2000 cases of invasive meningococcal disease in the United States, typically in the winter. The case fatality rate is high (up to 15%), with serious sequelae in up to 20% of those who survive. With the success of vaccines against other encapsulated organism (e.g., *S. pneumoniae*), *N. meningitidis* seemed an obvious target for a new vaccine.

The Vaccines

There are 2 broad categories of meningococcal vaccines, quadrivalent and bivalent. Quadrivalent vaccines target four different serotypes (subtypes A, C, Y, and W-135) of *N. meningitidis*.

Currently, there are 2 quadrivalent meningitis vaccines: MPSV4 and MenACWY. MPSV4 (brand name *Menomune*) is a polysaccharide vaccine and MenACWY (brand name *Menactra*) contains capsular polysaccharide antigens conjugated to diphtheria toxoid protein. MenACWY induces longer-lasting immunity, and in most cases is the preferred vaccine. When indicated, adults between ages 18-55 should receive the conjugated vaccine (MenACWY; *Menactra*). While MenACWY can be given to adults of any age, the ACIP recommends that adults over 55 who have not previously received MenACWY, should receive the polysaccharide vaccine (MPSV4; *Menomune*). The second, and newer category of meningococcal vaccine, is a bivalent vaccine which targets serogroup B. There are currently two serogroup B meningococcal (MenB) vaccines licensed for persons aged 10–25 years in the US, MenB-FHbp (brand name *Trumenb*) and MenB-4C (brand name *Bexsero*). In MenB-FHbp the vaccine creates antibodies to the outer membrane protein factor H binding protein (fHBP) and in MenB-4C three highly immunogenic antigens (fHbp, NadA and NHBA) were combined with outer membrane vesicles. In 2015, the ACIP recommended MenB vaccines for certain groups of persons aged ≥ 10 years and young adults aged 16–23 years to provide short-term protection against most strains of serogroup B meningococcal disease. There is no recommendation for MenB revaccination at this time.

Vaccine Indications

Rates of meningococcal disease are highest in infants, with a second peak in adolescence. College freshmen living in dormitories are also noted to be at higher risk than the general population. As with other encapsulated bacteria (e.g., *S. pneumoniae*), individuals with anatomic or functional asplenia, persistent complement component deficiencies, or with HIV infection should receive a 2 dose primary series of the MenACWY at least 2 months apart because they are at increased risk of infection with *N. meningitidis*. These patients should also be revaccinated every 5 years, due to the fact that they develop only modest antibody titers. Duration of immunity is also a concern for other patients receiving the meningococcal vaccine, so if their risk persists these groups of patients should undergo a two-dose primary vaccination schedule and be revaccinated every 5

years. Adults with anatomic or functional asplenia or persistent complement component deficiencies should also receive a series of MenB vaccine with either a 2- dose series of MenB-4C at least 1 month apart or a 3-dose series of MenB-FHbp at 0, 1-2, and 6 months. The two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses in a series. Adults with HIV are not recommended to receive the MenB vaccines because meningococcal disease in this population is primarily caused by serogroups C, W and Y. The two types of meningitis vaccines (MenACWY and MenB) may be administered at the same time but at a different anatomic site.

There are several other indications for meningitis vaccines:

1. ***Neisseria meningitidis* exposure:** Individuals that work with *Neisseria meningitidis* isolates should also receive a dose of the MenACWY every 5 years and also either the 2-dose series or the 3-dose series of the MenB vaccine.
2. **Meningitis outbreaks:** Adults at risk during meningitis outbreaks should receive a dose of MenACWY or the MenB series (2 or 3 doses) depending on the attributable serogroup.
3. **Travel:** Adults who travel or live in countries with hyperendemic or epidemic meningococcal disease should receive 1 dose of the MenACWY and be revaccinated every 5 years if the risk remains. MenB is not routinely indicated because meningococcal disease in these countries is generally not caused by serogroup B.
4. **Military recruits:** Military personnel should receive a dose of MenACWY every 5 years as long as increased risk for infection remains.
5. **College students:** First year college students aged ≤ 21 years who live in dorms should receive a dose of MenACWY if they have not received a dose after age 16.
6. **Healthy young adults:** Adults (18-23) who are healthy and not at increased risk for serogroup B meningococcal disease may receive either a 2-dose or 3-dose MenB series if they desire immunity.

A review of populations at risk is included in Table 10.

Table 10: Indications for the Quadrivalent Meningococcal Vaccine

Age 11-18	Age >18
All individuals	- Functional/anatomic asplenia (including sickle cell disease) - Complement deficiency (including deficiency in C3, C5-9, properdin, factor D, Factor H, or individuals taking eculizumab [Soliris]) - HIV infection - College freshmen living in dormitories - US military recruits - Those exposed during a meningitis outbreak - Travel to, or residence in countries in which <i>N. meningitidis</i> is hyperendemic or epidemic

Figure 3: Quadrivalent Meningococcal Vaccination and Revaccination

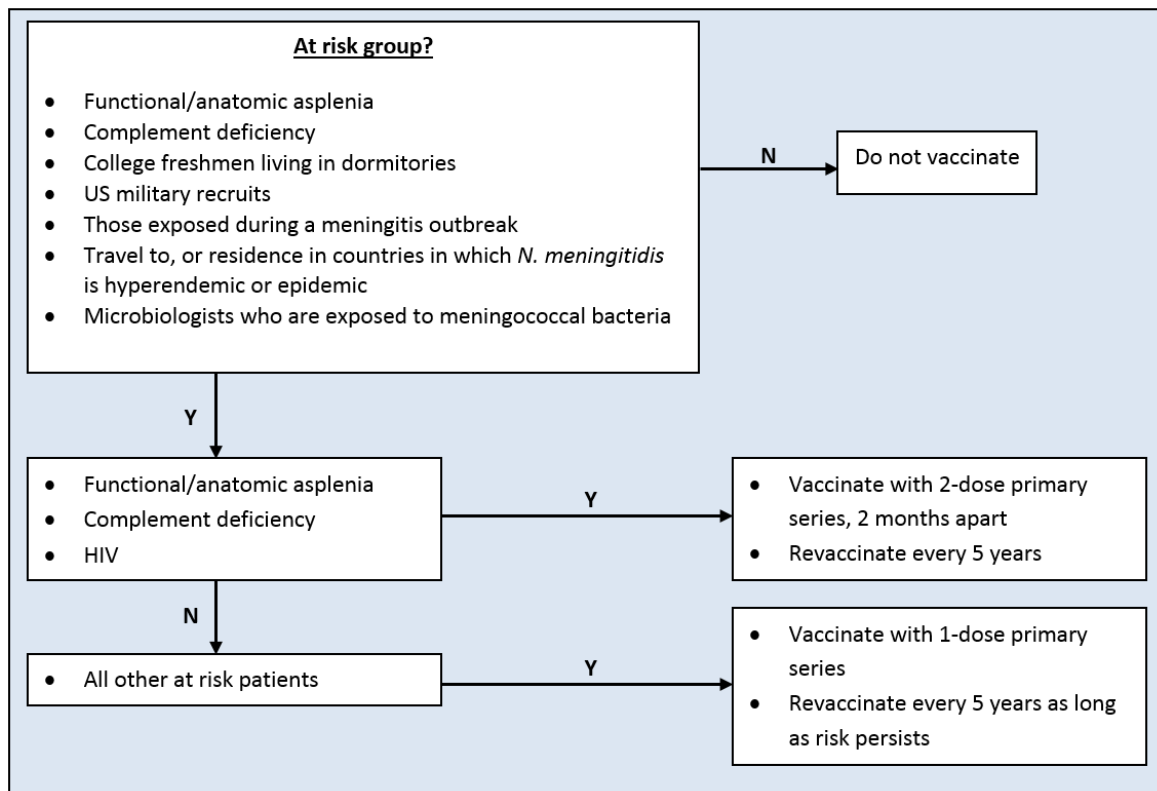
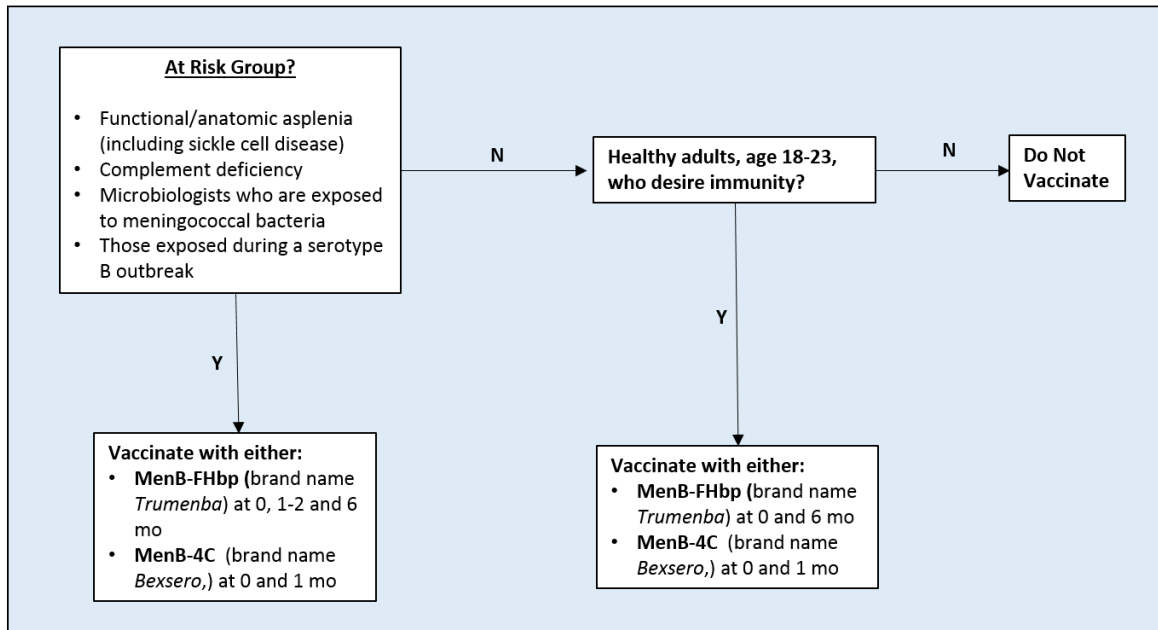


Figure 4: Bivalent (serogroup B) Meningitis Vaccination



Case 7: Objective: indications and contraindications for measles/mumps/rubella vaccine (MMR) vaccine.

Laertes, a 27-year-old passionate male who disapproves of his sister's unplanned pregnancy, is planning a trip to Denmark to help her. His past medical history is essentially unremarkable; he takes no medications. Other than issues with anger management, he is very healthy. Which one of the following statements about the measles/mumps/rubella (MMR) vaccine is true?

- A. Patients born prior to 1968 do not need to be vaccinated with MMR, as they are considered immune.
- B. He recalls having one MMR as a child; therefore he does not need another dose.
- C. Given his plan for international travel, Laertes should receive a total of 2 doses.
- D. Egg allergy is a contraindication to MMR.

Pop Up answers

- A. Incorrect. Adults born before 1957 are considered to have natural immunity to measles, mumps and rubella, and vaccination is not indicated. All adults born after 1957 who have no evidence of immunity should be vaccinated, unless a contraindication is present (e.g., pregnancy, cancer, or receiving high-dose corticosteroids).
- B. Incorrect. Persons in high-risk groups, such as healthcare personnel, students entering college, and other post-high school educational institutions should receive a total of 2 doses.
- C. Correct. International travelers should receive a total of 2 doses.
- D. Incorrect. Contraindications include: previous anaphylactic reaction to this vaccine or to any of its components, pregnancy or possibility of pregnancy within 4 weeks, and severe immunodeficiency.

Summary answer

The correct answer is **C: Given his plan for international travel, Laertes should receive a total of 2 doses.**

Measles/Mumps/Rubella Vaccine (MMR)

The MMR vaccine consists of **three live attenuated viruses**: measles, mumps and rubella.

Vaccination is usually performed in childhood, and is completed with a series of two vaccines.

Adults who were born before 1957 are considered immune to measles and mumps because of the prevalence of natural disease during their childhood; adults born after 1957 should have been immunized with 2 doses during childhood.⁴²

If there is no documentation of childhood immunization, or antibody titers are inadequate, MMR should be administered to any adult born after 1957. Particular attention should be paid to immunizing women of childbearing age (to avoid infection with rubella), but not to pregnant women (live-virus vaccines are not given to pregnant women). A single dose is typically adequate, with the exception of healthcare workers, college students or other post-high school educational institutions, and international travelers, who should receive two doses (doses are given at least 4 weeks apart). In addition, during a measles or mumps outbreak, a second dose is recommended. Individuals who were previously vaccinated with killed vaccine or unknown type of vaccine during 1963-1967 should also receive a second dose.

The MMR vaccine can interfere with skin testing for tuberculosis, and the MMR vaccine and tuberculin skin test (TST) should not be co-administered on the same day. If an MMR vaccine is administered, a planned TST should be delayed 4-6 weeks to avoid interference with the results.

The MMR vaccine is a live attenuated virus vaccine. It is therefore contraindicated in pregnant women, those with cancer, and those receiving high doses of corticosteroids (>20 mg of prednisone daily). Persons with HIV may be given MMR, but only if their CD4 is >200.³ MMR may be given with all other vaccines, but if not given on the same day as the other live vaccines, don't administer until at least 4 weeks have passed.³ Table 11 summarizes MMR indications and contraindications.

Table 11: MMR Vaccine Indications and Contraindications

MMR indications	MMR contraindications
• MMR is recommended for all adults born 1957 or later unless a contraindication is present or prior infection with measles or mumps was diagnosed ○ MMR (2 doses) should be given to unvaccinated adult healthcare workers born prior to 1957 in the setting of a measles or mumps outbreak and 1 dose MMR during a rubella outbreak ○ Women of childbearing age should be tested for rubella immunity, and vaccinated if not pregnant, or if pregnant, at completion or termination of pregnancy	• Pregnancy or likely to become pregnant within 4 weeks of vaccination • Immunocompromised (Note: MMR may be administered in those with HIV who have a CD4>200)
• A second dose of MMR is indicated if the patient is: ○ a student in a post-secondary educational institution ○ a healthcare worker ○ planning to travel internationally ○ exposed to measles in an outbreak setting ○ previously vaccinated with killed measles vaccine ○ vaccinated with an unknown type of measles vaccine during 1963-1967	

Section 8: Immunization review

Gertrude is a 63-year-old woman who comes to see you in October to update her health maintenance. She states she has recently remarried, and has recently had dyspepsia after accidentally swallowing a pearl that fell into her glass of wine. She and her husband both have chronic HIV infection; her most recent CD4 count was 800. She wants to protect herself, and requests every immunization that is medically indicated for her. She also has diabetes, controlled with metformin, but is not hypertensive, and is on no other medications. Physical examination is unremarkable. On review of systems, she last had a tetanus booster at age 18, when she entered college. Childhood immunizations are unknown.

Appropriate immunizations at this point would be:

- A. Td and influenza vaccines
- B. Tdap, MMR and influenza vaccines
- C. Td, MMR, pneumococcal vaccine
- D. Tdap, pneumococcal, and influenza vaccines

Pop Up Answers

- A. Incorrect. More vaccines are indicated.
- B. Incorrect. More vaccines are indicated.
- C. Incorrect. She does not require MMR. Given her age she is considered immune.
- D. Correct. She is due for a tetanus booster, and Tdap should be used. Because of her diabetes, pneumococcal and influenza vaccine are indicated. Because of her age, she is considered immune to measles, mumps, and rubella, thus MMR is not indicated (she was born before 1957).

Summary answer

The correct answer is **D: Tdap, pneumococcal, and influenza vaccines.**

In the final section of this module, we review all immunizations covered in the sections above.

Recommendations by age group

Regarding immunization recommendations, adults can be divided into three age groups: 18-49, 50-64, and 65 and older. Recall that those born before 1957 are considered immune to MMR.

Immunization recommendations vary among these groups as follows: For completeness, all standard vaccines are included in this listing. Those not discussed in this module are discussed in the Immunizations Module Part 2.

- **18-49 years old**
 - Td every 10 years for all persons in this age group (Tdap once in adult life).
 - Influenza annually.
 - MMR and varicella for those without documentation of vaccination or evidence of immunity.
 - Pneumococcal, hepatitis A, hepatitis B, and meningococcal vaccine for those at risk.
 - Repeat pneumococcal vaccine once for those at high risk.
 - Repeat meningococcal vaccine every 5 years for those at risk.
 - HPV vaccine for individuals aged 9-26.
- **50-64 years old**
 - Td every 10 years for all persons in this age group (Tdap once in adult life).
 - Varicella for those without documentation of vaccination or evidence of immunity.
 - Influenza annually.
 - Pneumococcal, hepatitis A, hepatitis B, and meningococcal vaccine for those at risk.
 - Repeat pneumococcal vaccine once for those at high risk and again at age 65 if >5 years since last vaccination.
 - Repeat meningococcal vaccine every 5 years for those at risk.
 - Zoster vaccine is FDA-approved for this age group, but not recommended by the Advisory Committee on Immunization Practices until age 60.
- **65 and older**
 - Td (Tdap once in adult life) every 10 years for all persons in this age group.
 - High dose influenza annually.

- Pneumococcal two-vaccine regimen: PCV13 at 65 (or one year after previous PPSV23 dose), PPSV23 8 weeks later (or 5 years after prior PPSV23 dose, whichever is later).
- Hepatitis A, hepatitis B and meningococcal vaccine for those at risk.
- Zoster vaccine once (ages 60 and older, if not given prior).

Contraindications Review

Live attenuated virus vaccines are contraindicated in certain populations. The commonly used vaccines that are live attenuated virus vaccines are MMR, varicella, zoster, and live attenuated influenza vaccine.

- **Contraindicated groups for the MMR vaccine**
 - Pregnant women.
 - Patients with immunodeficiency (i.e., malignancy, chemotherapy, high dose corticosteroids, congenital immunodeficiency, cochlear implant).
 - (Note that MMR may be administered to those with HIV as long as their CD4 is >200 cells/ml).
- **Contraindicated groups for the varicella vaccine**
 - Same as MMR, but in addition, varicella vaccine is contraindicated in all patients infected with HIV who have a CD4<200.
 - People with neomycin or gelatin allergy.
- **Contraindicated groups for the zoster vaccine**
 - Allergy to vaccine components, including gelatin and neomycin.
 - Immunocompromised persons
 - However, patients whose leukemia is in remission and who have not received chemotherapy (e.g., alkylating drugs or antimetabolites) or radiation for at least 3 months can receive zoster vaccine.
 - Persons infected with HIV who have a CD4<200.

- Persons on immunosuppressive therapy, including high-dose corticosteroids (>20 mg/day of prednisone or equivalent) lasting two or more weeks.
- Pregnancy, although these women are unlikely to be in the vaccine target age group.

- **Contraindicated groups for the live attenuated influenza vaccine**

- Pregnant women.
- People 50 years old and older.
- People with chronic pulmonary disease.
- People with chronic cardiovascular disease.
- People with chronic metabolic disease (e.g., DM, chronic renal disease).
- Immunocompromised patients (e.g., malignancy, chemotherapy, immune deficiency).
- People with a history of Guillain-Barre syndrome.
- People with egg allergy.

Table 12: Immunization Summary (see also Immunizations Part 2 module)

Figures 1 and 2 should be read with the footnotes that contain important general information and considerations for special populations.

Figure 1. Recommended immunization schedule for adults aged 19 years or older by age group, United States, 2017

Vaccine	19–21 years	22–26 years	27–59 years	60–64 years	≥ 65 years
Influenza ¹	1 dose annually				
Td/Tdap ²	Substitute Tdap for Td once, then Td booster every 10 yrs				
MMR ³	1 or 2 doses depending on indication				
VAR ⁴	2 doses				
HZV ⁵				1 dose	
HPV–Female ⁶	3 doses				
HPV–Male ⁶	3 doses				
PCV13 ⁷					1 dose
PPSV23 ⁷	1 or 2 doses depending on indication				1 dose
HepA ⁸	2 or 3 doses depending on vaccine				
HepB ⁹	3 doses				
MenACWY or MPSV4 ¹⁰	1 or more doses depending on indication				
MenB ¹⁰	2 or 3 doses depending on vaccine				
Hib ¹¹	1 or 3 doses depending on indication				



Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection



Recommended for adults with additional medical conditions or other indications



No recommendation

Table 13: Immunization Summary for Patients with Chronic Disease or Other Indications

Figure 2. Recommended immunization schedule for adults aged 19 years or older by medical condition and other indications, United States, 2017

Vaccine	Pregnancy ^{1,4,9}	Immu- compromised (excluding HIV infection) ^{7,11}	HIV infection CD4+ count (cells/ μ L) ^{3,7,9-11}		Asplenia, persistent complement deficiencies ^{7,10,11}	Kidney failure, end-stage renal disease, on hemodialysis ^{7,9}	Heart or lung disease, chronic alcoholism ⁷	Chronic liver disease ^{7,9}	Diabetes ^{7,9}	Healthcare personnel ^{8,9}	Men who have sex with men ^{6,8,9}
			< 200	$\geq$ 200							
Influenza ¹	1 dose annually										
Td/Tdap ²	1 dose Tdap each pregnancy	Substitute Tdap for Td once, then Td booster every 10 yrs									
MMR ³	contraindicated		1 or 2 doses depending on indication								
VAR ⁴	contraindicated		2 doses								
HZV ⁵	contraindicated			1 dose							
HPV-Female ⁶		3 doses through age 26 yrs									
HPV-Male ⁶		3 doses through age 26 yrs			3 doses through age 21 yrs						3 doses through age 26 yrs
PCV13 ⁷		1 dose									
PPSV23 ⁷		1, 2, or 3 doses depending on indication									
HepA ⁸	2 or 3 doses depending on vaccine										
HepB ⁹						3 doses					
MenACWY or MPSV4 ¹⁰			1 or more doses depending on indication								
MenB ¹⁰					2 or 3 doses depending on vaccine						
Hib ¹¹		3 doses post-HSCT recipients only		1 dose							

Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection
 Recommended for adults with additional medical conditions or other indications
 Contraindicated
 No recommendation

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