Optimal protection against preventable diseases for the pregnant woman and her fetus can be provided through vaccination prior to pregnancy. When indicated, however, the benefits of immunization during pregnancy and breastfeeding may outweigh the theoretical risks of potential adverse events. Several vaccinations recommended by the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC) can reduce maternal and fetal morbidity and mortality from preventable diseases. Physicians can maintain the highest standards of clinical practice by advocating for appropriate vaccinations in their female patients. The authors discuss current versions of CDC vaccination recommendations, contraindications, and precautions for pregnant and breastfeeding women.


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The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) annually update recommended immunization schedules for preventable diseases. The ACIP has noted a recent decrease in implementation of these vaccination schedules, leaving many individuals susceptible to preventable diseases. The American College of Obstetricians and Gynecologists (ACOG) notes that pregnant women represent a vulnerable population with regard to preventable diseases. An integral element of prenatal care should include an evaluation of the mother’s immunization status and administration of appropriate vaccinations. It is exceptionally important to vaccinate nonimmunized women to prevent further morbidity and mortality in mother and infant.

Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine Background

The Tdap vaccine immunizes against the pathogenic microorganisms of tetanus (Clostridium tetani), diphtheria ( Corynebacterium diphtheriae), and pertussis (Bordetella pertussis). The incidence of diphtheria is extremely low in the United States, with fewer than 5 cases reported since 2000. The incidence of tetanus is slightly greater than that of diphtheria. Approximately 70% of tetanus cases reported from 1980 to 2000 in the United States were in individuals older than 40 years, and only 2 cases of neonatal tetanus infections have been reported since 2000. A total of 18 tetanus cases were reported in 2009 in the United States.

Pertussis (ie, “whooping cough”) is of great concern because it persists despite vaccination efforts. Vaccination, which began in 1906, decreased the prevalence of pertussis by 80%. However, there has been a gradual increase in the incidence of this disease since 1976. From 2004 to 2008, pertussis was reported to cause 111 deaths in the United States, with 83% of these fatalities occurring in infants younger than 3 months. The most common complication and cause of death from pertussis infection is secondary bacterial pneumonia.

Pertussis infection during pregnancy has not been shown to increase morbidity in women. In limited case reports, no pertussis-related deaths have been
reported in pregnant women. Rare reports of fetal morbidity from infected mothers include a case of extradural hematoma and a case of laryngotraheal obstruction, but these fetal conditions were not found to be caused by the infection within the mother. Infants younger than 12 months appear to have the most severe pertussis-related morbidity and mortality. From 2000 to 2006, pertussis infections in infants younger than 12 months resulted in 145 deaths and 9078 hospitalizations. A majority of the infant deaths occurred in unvaccinated infants. A total of 15,632 cases of pertussis were reported in 2006, including 2029 cases in infants and 5045 cases in children aged 1 to 14 years. Fourteen of 16 pertussis-related deaths in 2006 occurred in infants. In 2009, 12 of 14 reported pertussis-related deaths were in infants younger than 6 months.

Considering this reported impact of pertussis on infant mortality, it is crucial to immunize mothers so that passive immunity is provided to fetuses. This passive immunity protects infants for the first 6 months of life, after which they can receive their first individual vaccinations.

**Available Vaccines**

Two Tdap vaccines were licensed in the United States in 2005: Adacel (Sanofi Pasteur Ltd, Toronto, Canada), for use in persons aged 11 to 64 years, and Boostrix (GlaxoSmithKline Biologicals, Rixensart, Belgium), for use in persons aged 10 years or older. Each vaccine is administered as a single dose.

**Recommendations**

The ACIP approved revised recommendations for use of the Tdap vaccine in pregnant women in June 2011. The US Food and Drug Administration (FDA) classifies the Tdap vaccine as a Pregnancy Category C drug, because there is insufficient evidence regarding safety of administration during pregnancy. Data are also insufficient regarding concerns of blunting the infant’s immune response with the combined diphtheria, tetanus toxoid, and acellular pertussis (DTap) vaccines. Nevertheless, the ACIP concluded that vaccinating pregnant women (who did not previously receive Tdap) in the late second trimester or third trimester is an acceptable risk for both mother and fetus. If immunization does not occur before or during pregnancy, a woman should receive 3 doses of Tdap after delivery at 0 and 4 weeks and at 6 to 12 months. The Tdap vaccine should replace 1 dose of tetanus-diphtheria vaccine within the DTaP series.

In addition, any adolescent or adult who anticipates having close contact with an infant younger than 12 months—and who has previously not received Tdap—should receive a single dose of Tdap at least 2 weeks before contact with the infant. The Tdap vaccine provides broad coverage of cellular immunity with a single dose. Details of the ACIP recommendations for prevention of pertussis, tetanus, and diphtheria among pregnant and postpartum women and their infants are shown in Figure 1.

The revised ACIP recommendations are in line with the CDC’s strategy for reducing the burden of pertussis disease in infants in the United States. Implementation of a Tdap vaccination program should be initiated by a pregnant woman’s physician. The ACCG’s Committee on Obstetric Practice supports the revised ACIP recommendations on use of the Tdap vaccine during pregnancy.

**Adverse Events**

The most common adverse events reported within 14 days of administration of the Tdap vaccine were pain, erythema, swelling, and fever. Fewer than 1% of the individuals who reported these adverse events sought medical attention for the reactions.

**Contraindications and Precautions**

A severe allergic reaction (eg, anaphylaxis) after a previous dose of Tdap vaccine or any other vaccine in the DTaP series is a contraindication to vaccination. In such cases, none of the vaccine components should be administered because of uncertainty as to which component is responsible for the adverse reaction. However, if further immunizations are desired, such individuals may be referred to an allergist for evaluation.

If Guillain-Barré syndrome (GBS) developed in a patient within 6 weeks of receiving a previous vaccine containing tetanus toxoid, the decision to use the Tdap vaccine should be based on careful consideration of potential benefits vs possible risks. It should also be kept in mind that the tip caps of prefilled syringes of Tdap may contain natural rubber latex, which may cause allergic reactions in latex-sensitive individuals.

**Influenza Vaccine Background**

Infection with influenza type A or influenza type B viruses triggers the acute respiratory disease of influenza. These viruses are single-stranded RNA viruses with the helical shape that is characteristic of the Orthomyxoviridae family. Smith, Andrews, and Laidlaw initially isolated influenza type A virus in 1933 in ferrets, and Francis isolated the influenza type B virus in 1936. Also in 1936, Burnet discovered that the influenza virus could be replicated inside eggs—a finding that led to the development of inactivated influenza vaccines by the 1950s.

There have been multiple influenza pandemics throughout history, with the earliest one described in 1580. The Spanish influenza pandemic of 1918-1919 was responsible for approximately 21 million deaths worldwide. Since 1977, 2 subtypes of seasonal influenza A (ie, H1N1 and H3N2) have circulated among humans globally.

The US influenza pandemic of 2009-2010 began in April 2009 with a novel H1N1 virus that quickly spread across North America. By May 2009, the virus had spread to many other areas of the world, with peak incidence in October 2009. A gradual decline in incidence was reported through January 2010. Public health authorities estimate that 60 million Americans were infected with the H1N1 virus in the 2009-2010 season, leading to more than 270,000 hospitalizations and 12,500 deaths. A monovalent vaccine was distributed as a part of the national vaccination program.

In 2009, pregnant women at increased risk for severe illness and complications from seasonal influenza were investigated by the New York City Department of Health and Mental Hygiene. Using active and passive surveillance for cases of H1N1 infections, the department found that pregnant
women with infections were 7.2 times more likely to be hospitalized and 4.3 times more likely to be admitted to an intensive care unit than were nonpregnant women.18

Figure 1. Recommendations of the Advisory Committee on Immunization Practices for the prevention of pertussis, tetanus, and diphtheria among pregnant and postpartum women and their infants. Revisions in the recommendations made in 2011 are consistent with these recommendations, which were originally published in 2008.8 Reprinted with permission from ACOG Committee on Obstetric Practice. ACOG Committee Opinion No. 438: update on immunization and pregnancy: tetanus, diphtheria, and pertussis vaccination. Obstet Gynecol. 2009;114(2 pt 1):398-400. Abbreviations: DTaP, combined diphtheria, tetanus toxoid, and acellular pertussis vaccine; DTP, combined diphtheria, tetanus toxoid, and pertussis vaccine; Td, tetanus-diptheria vaccine; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis antigens.

Influenza viruses replicate and mutate via antigenic drift, in which the replication process is disrupted by random point mutations and recombinations that could increase infectivity and lead to further pandemics.20 Vaccines to any strain of influenza virus provide little or no cross-immunity to other strains, which is why the influenza strains in circulation must be evaluated yearly and the vaccine formulations must be adjusted in anticipation of the strains for the following season. This process necessitates the need for annual immunizations.

Pathogenicity of influenza occurs via respiratory transmission, allowing viral attachment to respiratory epithelium. The virus then penetrates epithelial cells and replicates within the host cells, resulting in cellular destruction.

Incubation of the influenza virus occurs over 1 to 4 days, with peak viral shedding occurring 1 day before and 3 days after symptom onset.18 High viral shedding may persist for 5 to 10 days in respiratory secretions.15 Approximately half of influenza infections result in the classic symptoms of abrupt onset of fever (usually 101°F-102°F), myalgia, sore throat, nonproductive cough, and headache. Other symptoms may include rhinorrhea, headache, substernal chest burning, and ocular problems (eg, eye pain, sensitivity to light).15

Available Vaccines
There are 2 main forms of the influenza vaccine: the trivalent inactivated influenza vaccine (TIV) and the live attenuated influenza vaccine (LAIV). (A list of the influenza vaccines approved by the FDA for the 2011-2012 season is shown in the article by Foster and Nevin-Woods in this JAOA supplement issue.) Because LAIV has the potential to cause mild signs and symptoms related to the infection, it is contraindicated in pregnancy. The live attenuated influenza vaccine is licensed for use in nonpregnant patients aged 2 to 49 years.20 The FDA classifies TIV as a Pregnancy Category C drug because no adequate animal reproductive studies of the vaccine have been completed, and current data are insufficient regarding whether the influenza vaccine causes fetal harm when
administered to pregnant women.

Multidose vials of the influenza vaccine have been manufactured with thimerosal, a mercury-containing preservative added to prevent bacterial growth. The only adverse effects associated with vaccines containing thimerosal are occasional local skin reactions at the site of vaccination.20 There is no scientific evidence of adverse effects in children born to women who received thimerosal-containing vaccines.20 The ACIP does not indicate a preference for either thimerosal-containing or thimerosal-free vaccines in any group, including pregnant women, because the benefits of vaccination for all recommended groups outweigh concerns about theoretical risks of thimerosal exposure.20

Recommendations
The ACOG’s Committee on Obstetric Practice agrees with the ACIP recommendation that all women who will be pregnant through the influenza season (ie, October through May in the United States) should receive TIV.21 Pregnant women may be vaccinated at any gestational age. It is more beneficial to receive the vaccination earlier in the influenza season than later in the season.

There have been no studies showing adverse outcomes from TIV in pregnant women or their infants.21 A retrospective cohort study in Nova Scotia compared rates of hospital admissions and physician visits because of respiratory illness among pregnant women during influenza season with rates for the same women during the influenza season before their pregnancies.22 Pregnant women were more likely than non-pregnant women to have higher rates of hospital admissions and physician visits for respiratory illness. The hospitalization and physician visit rates were highest among women who were infected with influenza during the third trimester.22

The researchers in Nova Scotia noted that their data supported recommendations that pregnant women with comorbidities, regardless of pregnancy stage, receive influenza vaccination during influenza season.22 However, a 1999 survey of obstetricians and gynecologists concluded that only 39% of respondents administered influenza vaccines to obstetric patients in their practices—although 86% of respondents agreed that pregnant women are at increased risk for influenza-related morbidity and mortality.23

After pregnant women are vaccinated, they produce circulating antibodies against influenza. These anti-influenza antibodies have been found to be transferred to the fetus through the blood and breast milk, possibly conferring protection to the newborn until age 6 months, when the infant may be vaccinated.20 A study published in 2008 found that infants born to vaccinated women who breastfed for a mean duration of 14 weeks had a 63% reduction in laboratory-confirmed influenza illness during the first 6 months of life.24 However, a retrospective analysis of clinical records conducted from 1997 to 2002 did not find a reduction in influenzalike illness among vaccinated pregnant women or their infants.25 In a study conducted from 1995 to 2001, medical visits for respiratory illness among infants were not reduced substantially if their mothers had been vaccinated against influenza during pregnancy.26

Details of ACIP recommendations for annual influenza vaccination are shown in Figure 3.15,16

Adverse Events
The most common adverse events associated with use of the influenza vaccine in adults were pain and redness at the injection site, muscle aches, fatigue, and headache. Such adverse events occurred in 10% of cases.27 In addition, 10% of children aged 5 to less than 18 years experienced swelling at the injection site. Ten percent of children aged 3 to less than 5 years observed pain, redness, and swelling at the injection site, as well as irritability, loss of appetite, and drowsiness.27

Allergic reactions—though rare—from influenza vaccination have been observed in the form of hives, angioedema, allergic asthma, and systemic anaphylaxis.27 Influenza vaccine formulations are produced within chicken eggs and, after processing, may contain a small quantity of egg protein, which can induce hypersensitivity symptoms. In 1976, the swine influenza vaccine was associated with an increased frequency of GBS. However, no subsequent evidence has shown a causal relationship of GBS with influenza vaccines.27

Contraindications and Precautions
The trivalent inactivated influenza vaccine is contraindicated in any individual with known anaphylactic hypersensitivity to eggs or to other components of
Annual influenza vaccination is recommended for persons aged 6 months or older who are at increased risk for influenza-associated complications and persons (such as healthcare providers and household contacts) who have close contact with high-risk individuals. Individuals at high risk for severe influenza-related complications include the following:

- Persons aged 65 years or older
- Residents of nursing homes and other long-term care facilities that house persons of any age with chronic medical conditions
- Adults and children with chronic pulmonary or cardiovascular disorders, including asthma
- Adults and children who required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications)
- Adults and children who have a condition (eg, cognitive dysfunction, spinal cord injuries, seizure disorders, other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk of aspiration
- Children and adolescents (age 6 months-18 years) who are receiving long-term aspirin therapy and, therefore, might be at risk for developing Reye syndrome after influenza
- Women who will be pregnant during the influenza season
- Children aged 6 to 23 months

Annual vaccination is also recommended for the following persons because of increased risk of visits to influenza-associated clinics, emergency departments, or hospitals, particularly if they have high-risk medical conditions:

- Children aged 24 to 59 months
- Adults aged 50 to 64 years
- Adults aged 65 years and older

To prevent transmission of influenza to persons at increased risk of influenza-related complications, vaccination is also recommended for the following persons:

- Household contacts and out-of-home caretakers of persons at high risk of severe complications from influenza, and contacts and caretakers of children younger than 5 years, particularly infants younger than 5 months. (Although the pediatric group at greatest risk of influenza-related complications consists of infants younger than 6 months, the Food and Drug Administration has not approved influenza vaccines for use in this group.)
- Healthcare workers

Figure 3. Recommendations of the Advisory Committee on Immunization Practices for annual influenza vaccination.15,16

The influenza vaccine—unless the recipient has been desensitized. For any individual who has moderate to severe acute illness, vaccination can be given after the individual’s condition has improved.30

Breastfeeding is not considered a contraindication to influenza vaccination. Thus, women who are breastfeeding may receive the influenza vaccine.20

Human Papillomavirus Vaccine

Background

The most common sexually transmitted infection in the United States is genital human papillomavirus (HPV). Approximately 6.2 million people in the United States are newly infected with HPV each year.28 These infections are associated with genital warts and cervical cancer—a causative association that was confirmed in epidemiologic studies in the 1960s and in cellular studies in the 1980s.29

Of 100 or more genotypes of HPV, more than 40 are found within the genital tract26 and 15 of them are associated with cervical cancer.30 Types 16 and 18 have been found to cause approximately 70% of cervical cancer cases, and types 6 and 11 cause approximately 90% of the cases of genital warts and respiratory papillomatosis.30

Despite implementation of cervical cytology screening programs and treatment for precancerous lesions, about 50% of patients newly diagnosed as having cervical cancer have never received a Papanicolaou (Pap) test.30 An additional 10% of patients newly diagnosed as having cervical cancer have not received a Pap test within the past 5 years.30

Available Vaccines

The FDA approved the first quadrivalent HPV (HPV4) vaccine (Gardasil; Merck & Co Inc, Whitehouse Station, NJ) in June 2006 for prevention of infections caused by HPV types 6, 11, 16, and 18 in girls and women aged 9 to 26 years.31

The first bivalent HPV (HPV2) vaccine (Cervarix; GlaxoSmithKline Biologicals, Rixensart, Belgium), for protection against HPV types 16 and 18, became FDA approved in October 2009 for girls and women aged 10 to 25 years.32 Neither vaccine is a live vaccine. Rather, both are made of viruslike particles derived from the recombinant L1 capsid protein of HPV.33

Recommendations

The ACOG endorses the ACIP’s recommendations for HPV vaccination.30 The goal of vaccination is to achieve immunity before potential exposure to HPV through sexual contact. The ACIP recommends routine vaccination of girls aged 11 or 12 years, with 3 doses of either the HPV4 or HPV2 vaccine.34 This age group was selected because studies suggest that the HPV4 vaccine is safe and effective, with high antibody titers, for girls of these ages. Other contributing factors to selection of this age group included data on epidemiologic characteristics of HPV, on age of sexual debut, and on the probability of HPV acquisition.34

The HPV vaccines are administered intramuscularly, with the second dose following the initial dose by 1 to 2 months.30 The third dose is given 6 months after the initial dose. Girls and women aged 13 to 26 years who did not receive the vaccine at the recommended age of 11 or 12 years should receive catch-up vaccination. The vaccine series can
be started as early as age 9 years and is FDA approved until age 26 years. However, if the vaccine series was started before age 26, the series may be completed beyond this age. If an interruption occurs in the dosing schedule, the vaccine series does not need to be restarted—regardless of time between doses—but the series should be completed.

The ACIP recommends either the HPV2 or HPV4 vaccines for prevention of cervical precancerous lesions and cervical cancers, and the committee notes that the HPV4 vaccine may confer further immunity to other HPV-related cancers. Studies support the use of the HPV4 vaccine for protection against vulvar and vaginal cancers and precancers and prevention of genital warts. However, there are insufficient data to recommend the HPV2 vaccine for these other conditions.

Special considerations regarding HPV vaccination include women with abnormal results from cervical cancer screening and women who have already had genital warts and are likely to have been exposed to HPV. These individuals need to be counseled that vaccination may not be effective for them. Nevertheless, vaccination is still recommended for these women because the HPV types that they have acquired may differ from the types in the vaccine.33 Prevaccination cervical screening is not recommended at any age.33 Studies are under way to determine if the recommended ages for HPV vaccination should be extended beyond 26 years.

The FDA classifies both HPV vaccines as Pregnancy Category B drugs (ie, drugs with no evidence of risk in pregnancy).31,32 However, HPV vaccination is not recommended for pregnant women because although there is no evidence that the vaccines cause harm to the fetus, there is no need to expose the fetus to something that provides no benefit to it. Furthermore, to our knowledge, no studies have been performed regarding potential risks to the fetus if the vaccine is received during pregnancy.

Women receiving HPV vaccines should be counseled to use contraception if they are sexually active. The vaccine manufacturers maintain pregnancy registries for individuals who become pregnant after vaccination.31,32 If a woman conceives or was already pregnant during a vaccination series, no intervention with the pregnancy is necessary, and the vaccination schedule should be resumed after pregnancy is completed.30,33

The ACOG notes that the HPV vaccines are made from inactivated viruses, and therefore they do not affect the safety of breastfeeding for mothers or infants.30

**Duration of Immunity**

Current data suggest that the duration of immunity provided by HPV vaccines ranges from 3.6 to 6 years. A multinational phase III trial of HPV4 vaccination found up to 100% reduced risk of high-grade cervical, vulvar, and vaginal lesions related to HPV types 16 and 18, and of genital warts related to HPV types 6 and 11, over an average of 3.6 years (and a maximum of 4.9 years).35

The Nordic Long-Term Follow-Up Study demonstrated that vaccinating adolescents prior to sexual debut provides durable protection from persistent infection caused by HPV types 6, 11, 16, and 18 for a period of 6 years after vaccination.36 The study found no breakthrough cases of persistent infection or disease related to HPV vaccination.36 Those study results highlight the importance of early HPV vaccination as a priority in the care of female patients.

**Expanding HPV4 Vaccination Indications**

In October 2009, the FDA approved the HPV4 vaccine for use in males aged 9 to 26 years to prevent the acquisition of genital warts. The ACIP concluded that the vaccine may be given to boys and men to “reduce the likelihood of acquiring genital warts,” though the committee does not recommend routine immunization with the HPV4 vaccine in males.37

In December 2010, the FDA expanded its approval of the HPV4 vaccine to include prevention of anal intraepithelial neoplasia in males and females aged 9 through 26 years.31 The FDA also approved the vaccine for the prevention of anal cancer caused by HPV types 16 and 18 in males and females aged 9 through 26 years.31

As of October 2011, ACIP discussions were ongoing regarding the cost-effectiveness of implementing recommendations for HPV vaccination in boys and men. Although cost-effectiveness has been shown to be beneficial in vaccinating females, there is no consensus as to the benefit of routine vaccination in males.38 Thus, additional data are required for further analysis.

The impact of vaccination in preventing oropharyngeal cancers caused by HPV type 16 is also being examined by the ACIP.39 Such tumors have been found to be distinct from HPV-negative head and neck cancers. Oropharyngeal cancers caused by HPV infections are increasing in the United States and other countries.39 The ACIP notes that no studies have shown direct evidence that the HPV vaccine protects against oral HPV infection, but additional investigation is required.

**Adverse Events**

The most common adverse events associated with HPV vaccination are headache, fever, nausea, and dizziness, as well as local reactions at the injection site (eg, bruising, erythema, pain, pruritus, swelling).40 Syncope has also been noted, with some cases associated with tonic-clonic movements and other seizure-like activity.40 Observation of the patient for at least 15 minutes after vaccine administration is recommended to prevent injury from falling during a syncopal episode.30

**Contraindications and Precautions**

The HPV4 vaccine is contraindicated in individuals with histories of immediate hypersensitivity to any vaccine component or to yeast.31 (The HPV4 vaccine is produced in *Saccharomyces cerevisiae* [baker’s yeast].) The HPV2 vaccine is contraindicated in individuals with anaphylaxis to latex, because the prefilled syringes have latex in the rubber stopper. The single-dose vials of HPV2 vaccine do not contain latex.33

The HPV vaccines can be given to individuals with minor acute illness, but vaccination should be postponed if illness is moderate or severe until the individual’s condition improves.33 The vaccines can also be given simultaneously or
at any time before or after administration of a different inactivated vaccine or a live vaccine. Although HPV vaccines are not recommended for use in pregnant women, they may be safely used in women who are breastfeeding. A summary of key information on the HPV vaccines, including contraindications and precautions, is shown in Figure 4.

State laws vary regarding HPV vaccination of minors. Legislation has been introduced in numerous states to require the HPV vaccine for girls in school. Requirements regarding the need for parental consent for a minor to receive HPV vaccination also vary by state. Physicians must know and follow their state laws when providing HPV vaccination or other healthcare to minors.

Conclusion
There exists a disparity between physician knowledge of the importance of immunization and physician use of vaccinations for their patients. This inconsistency in physician practices has contributed to the resurgence of various preventable diseases. The impact of the reemergence of these diseases has led to increases in morbidity and mortality among women and infants, as well as to a major financial burden on society.

It is imperative that physicians, healthcare organizations, and public health officials continue efforts to improve the rate of immunization in the United States. Therefore, it is the responsibility of primary care physicians—those practicing family medicine, internal medicine, obstetrics and gynecology, or pediatrics—to educate and vaccinate their patients based on the current recommendations of the ACIP, the ACOG, the American Academy of Family Physicians, and the American College of Physicians.

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