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Influenza and Tetanus, Diphtheria, and Acellular Pertussis Vaccinations During Pregnancy

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Vaccinations in pregnancy are an important aspect of prenatal care and of improving not only maternal health but also neonatal outcomes. Only 2 vaccines are specifically recommended during pregnancy: influenza and tetanus, diphtheria, and acellular pertussis (Tdap).

Because influenza illness disproportionately affects pregnant women compared with other populations, annual prevention of influenza illness is recommended for all women who will be pregnant during influenza season (October to May). Influenza vaccination has been recently reported to also result in decreased febrile respiratory illnesses in the newborn, likely through passive antibody transfer.

Pertussis infection rates are rising in the United States as vaccine-induced immunity wanes, with the mortality burden primarily seen in infants aged <6 months. Pertussis immunization with Tdap is now recommended for all pregnant women during the late second (>20 weeks) or third trimester with the intent to both protect the pregnant woman and provide passive antibody to the infant before vaccination at 2 months of age.

Provider support for these recommendations regarding both annual influenza vaccination and postpartum Tdap vaccination during pregnancy is critical to ensuring vaccine delivery and improving both maternal and fetal health. The article reviews the epidemiology and clinical aspects of influenza and pertussis infection with particular attention to pregnancy and recommendations for vaccination in these women.

Target Audience: Obstetricians and gynecologists, ophthalmologists, neurologists, family physicians, emergency room physicians

Learning Objectives: After completing this CME activity, obstetricians and gynecologists should be better able to analyze how influenza infection disproportionally affects pregnant women. Assess how influenza vaccination improves maternal and likely neonatal outcomes. Evaluate pertussis infection and immunity in adults, and counsel pregnant women as to the benefits of Tdap vaccination, particularly for the infant.

ROUTINE IMMUNIZATIONS

According to the Infectious Disease Society of America and the Centers for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP), the only vaccines routinely recommended for use during pregnancy are adult-type tetanus and reduced diphtheria toxoids combined with acellular pertussis vaccine (Tdap), and inactivated influenza vaccines.¹ Although published guidelines for immunization of pregnant women state that immunizations during pregnancy may be delayed until the second or third trimester, to minimize theoretical concerns about teratogenicity or miscarriage resulting from the vaccine or toxoid, there are no known risks to their
administration during the first trimester. Patients with unique exposures or required travel or other medical risks may qualify for further immunizations. Finally, postpartum women should receive all vaccines that were not given during pregnancy.\(^1\)

**INFLUENZA**

**Influenza Virology**

The influenza virus is a ribonucleic acid virus in the family of Orthomyxoviridae and infects both birds and mammals. Influenza viruses circulate globally, resulting in yearly seasonal outbreaks. In the United States alone, an average of 41,000 people die annually from complications of influenza.\(^2\)

There are 3 types of influenza virus: influenza virus A, influenza virus B, and influenza virus C. Although aquatic birds are the natural hosts for the influenza A virus, influenza A infections are common in humans and often cause severe disease. Influenza B virus is almost exclusively a human pathogen and mutates at a slower rate than influenza A.\(^3\) Influenza C virus can infect humans, pigs, and dogs, but is much less common than the other 2 serotypes and is often a self-limiting mild illness in children.\(^4\)

The structure of the influenza virus is characterized by a segmented genome that frequently reassorts and mutates, creating new antigenic variants. Two large glycoproteins are on the surface of the viral particles, hemagglutinin and neuraminidase. These surface proteins are the basis for the H and N distinctions giving influenza strains their names, such as H3N2 or H1N1.\(^5\)

**Influenza Infection**

Clinical symptoms of influenza infection include fever, cough, rhinorrhea, sore throat, headache, and myalgia, with the clinical manifestations in pregnant women being similar to those seen in the general population. Overall, influenza and its complications lead to an average of 200,000 hospitalizations and 36,000 deaths annually.\(^6\) Susceptible groups include children aged ≤5 years, adults aged ≥50 years, and those with chronic medical conditions; these groups comprise much of the influenza-related morbidity and mortality. Pregnant women are also at significant risk for serious sequelae from influenza infection, including hospitalization and death.\(^7\) During the 1918 and 1957 influenza pandemics, rates of influenza-associated deaths were higher among pregnant women than other populations.\(^8,9\) Therefore, prevention of influenza illness among pregnant populations through vaccination is critical and recommended by the CDC-ACIP and by American College of Obstetricians and Gynecologists.\(^10\)

The rapid diagnosis of influenza is problematic using bedside diagnostic methods, as they are not sensitive enough to definitively rule out influenza. Sensitive molecular methods are becoming more widely available, but in their absence, prompt antiviral therapy should be used to reduce the burden of disease in the pregnant woman with suspected influenza.

**Historical Influenza Pandemics**

Although poorly documented in the literature, experts at the National Institutes of Health propose that the year 1510 marked the first recognized influenza pandemic. It is speculated that during the 16th century, influenza came to be recognized as a distinct condition of acute onset characterized by fever, headache, cough, and myalgia, with uncommon complications including pneumonia and fatal outcomes in pregnant women and their fetuses. In the 20th century, the Spanish flu of 1918 was particularly severe, killing 50 to 100 million people, an estimated 3% of the entire world’s population. The Spanish flu was the first of 2 pandemics involving the H1N1 influenza virus (1918 and the recent 2009 H1N1 pandemic). Influenza vaccine was first developed in the 1940s and has been shown to be effective in reducing laboratory-confirmed influenza disease in various populations. Currently, yearly influenza vaccination is recommended for the entire population in the United States, including pregnant women.

**Importance of Influenza Vaccination**

The influenza vaccine consists of influenza viruses that are predicted will circulate in the upcoming influenza season, with frequent changes to account for the antigenic drift occurring naturally in the influenza viruses. The trivalent inactivated influenza vaccine is given intramuscularly and is recommended for all women who will be pregnant during the influenza season, regardless of gestational age. In contrast, the live attenuated influenza vaccine (LAIV, FluMist) is not licensed for use in pregnant women. Women can receive the LAIV in the postpartum period. However, because of viral shedding, there is a possibility that a mother may infect her neonate, and the LAIV is generally avoided for postpartum women.

An example of the importance of influenza vaccination came from the 2009 H1N1 pandemic season,
when the CDC identified pregnant women as a “vulnerable population” at the top of the priority list for receipt of vaccine. Moving from national guidelines to clinical care, vaccination of pregnant women has been recommended for >50 years. Despite a documented benefit in reduction of influenza-related respiratory illnesses and health care provider visits among all ages and demographic characteristics, influenza vaccination rates in the United States are historically poor. Before 2009, the vaccination rates among pregnant women were reported as 13% to 34%. (Fig. 1). Using patient self-reporting, polls, and surveys, real-time information obtained during the 2009–2010 influenza season indicated improved vaccination rates in 2009–2010. Seasonal influenza vaccination rates ranged between 32% and 64%, and H1N1 flu vaccination rates were between 42% and 54%.

Maternal vaccination with inactivated influenza virus is the most effective tool in reducing febrile respiratory infections among pregnant women. In addition, a recent retrospective cohort analysis using data from the Georgia Pregnancy Risk Assessment Monitoring System found reduced rates of preterm birth (OR: 0.6, 95% CI: 0.38–0.94) and small for gestational age infants (OR: 0.31, 95% CI: 0.13–0.75) among women receiving influenza vaccine over the 2006–2007 and 2007–2008 influenza seasons. Although limited by survey recall and small numbers, these findings support the impact of maternal vaccination on fetal outcomes.

Further, the strategy of “cocooning” the infant aged <6 months is being explored. The concept of cocooning involves protection of the newborn via vaccination of mothers, family members, and individuals in close contact with the newborn infant. The CDC-ACIP currently recommends vaccinating household contacts and out-of-home caregivers to reduce the risk for influenza in infants aged <6 months, given that there is currently no FDA-licensed vaccine for use in this population. Halasa et al reported that infants aged <6 months failed to mount an adequate immune response to influenza vaccine because of the presence of maternal antibody. However, a recently published randomized trial of influenza vaccination of pregnant women in Bangladesh found that vaccine was not only effective in preventing maternal febrile respiratory illness but also reduced the incidence of proven influenza illness by 63% in infants up to 6 months of age. Unfortunately, compliance with vaccination guidelines for household contacts of newborns has been fairly poor.

**Treatment of Influenza Illness**

Initiation of treatment for a mother with febrile respiratory illness suspected to be influenza should be prompt and not based on rapid antigen testing results. Pregnant and postpartum women (up to 2 weeks) with suspected or confirmed illness from influenza should be promptly treated with oseltamivir (Tamiflu). Oseltamivir dosing is 75 mg orally twice daily for 5 days; however, for hospitalized patients, a longer course may be required. Up to one-third of women hospitalized with influenza will develop a superimposed bacterial pneumonia requiring antibiotic treatment. Supportive care with antipyretics, bronchodilators, or decongestants should also be used in accordance with clinical scenario and patient co-morbidities.

![Fig. 1. Coverage estimates by influenza season, United States—adults aged ≥18 years. Among adults aged ≥18 years, the 2010–2011 monthly coverage estimates of influenza vaccine were similar to the 2009–2010 monthly seasonal (trivalent) coverage. (Source: http://www.cdc.gov/flu/professionals/vaccination/coverage_1011estimates.htm. Accessed 11/2011).](http://www.cdc.gov/flu/professionals/vaccination/coverage_1011estimates.htm)
BORDETELLA PERTUSSIS

Pertussis Bacteriology

Pertussis (whooping cough) is an acute, prolonged respiratory illness caused by the gram-negative organism, *Bordetella pertussis*. Infection is spread among immunocompetent adolescents and adults with waning vaccine-induced immunity, unimmunized children, and immunocompromised individuals who respond poorly to vaccination. Although typically associated with childhood illnesses, it is being increasingly recognized among adults.

The incubation period for pertussis is usually <10 days, but can vary from 1 to 3 weeks. Acute infection is classically separated into 3 phases: catarrhal, paroxysmal, and convalescent.

Pertussis Clinical Symptoms

Classic Description of the 3 Phases

- The catarrhal phase (initial 1 to 2 weeks) is characterized by rhinorrhea, conjunctival injection, general malaise, low-grade fever, and mild cough. These features are so similar to other viral upper respiratory infections (URI) that the diagnosis of pertussis, in its earliest phase, is challenging. As the cough worsens, the paroxysmal phase is entered.
- The paroxysmal phase (may last between 1 and 6 weeks, but can be as long as 10 weeks) is characterized by bursts of rapid coughs followed by a long inspiratory gasp, which may sound like a “whoop.” In young infants, the “whoop” may be replaced by apneic episodes. Adults may lack the characteristic “whoop.” These bursts of rapid coughs occur more often at night, increasing in frequency over the first 1 to 2 weeks and not diminishing until 3 to 5 weeks later. These coughing episodes are often associated with diaaphoresis, flushing, posttussive emesis, and fatigue. After the paroxysmal phase, there is transition into the convalescent phase.
- The convalescent phase is characterized by gradual resolution of the cough. However, another upper respiratory infections or irritants may cause recurrence of the coughing spells.

Modifications of the Classic Presentation for the Adolescent or Adult

Adolescents and adults may not display the typical phases and features of pertussis, likely because of partial immunity, whether from prior infection or vaccination. These individuals will frequently have prolonged, persistent coughing episodes that are easily confused with acute bronchitis. Profuse sweating and posttussive emesis are associated with the paroxysms of cough, occurring in nearly half the cases. The “whoop” is present in only a minority of patients. The illness is worse among smokers and those with asthma. Although clinically milder among adults, an average of 7 days loss of work is common, as well as sleep disturbances up to 2 weeks.

Pertussis Infection

Among adults and adolescents, the index of suspicion for pertussis must be high to make a prompt diagnosis. Early treatment may lessen the severity of the clinical course, or more importantly, prevent spread of infection within the community. Infected adults have been identified as an important reservoir for *B. pertussis* infection in young children.

The differential diagnosis includes a variety of respiratory illnesses, both viral and bacterial. Complications seen in adults and adolescents include incontinence, rib fracture, hernia, and back pain.

Diagnosis is based on clinical suspicion and confirmed by laboratory tests. The WHO and CDC both define a clinical case as coughing illness lasting at least 2 weeks accompanied by one of the following: paroxysms, whoop, or posttussive emesis (CDC, WHO, CDC). Many authorities and the CDC recommend combinations of diagnostic tests based on the length of cough present (see later in the text). Confirmed cases should be reported to local health departments.

- In the first 2 weeks after start of cough—bacterial culture plus polymerase chain reaction.
- Cough for 3 to 4 weeks—polymerase chain reaction and serologic testing.
- Cough for >4 weeks—single serologic testing.

Treatment with macrolides is indicated for both therapy and postexposure chemoprophylaxis of household contacts and other close contacts, regardless of vaccination status. Cases with cough for <3 weeks may be treated with either a 14-day course of erythromycin or a 5-day course of azithromycin. Treatment regimens include azithromycin, erythromycin, or clarithromycin, reserving sulfamethoxazole/trimethoprim (Bactrim) for those who are macrolide allergic. The administration of antibiotics at >3 weeks into the illness does not likely affect the course of symptoms, but it is warranted to help reduce spread of infection. Unfortunately, most cases of pertussis remain infectious for up to a month;
However, individuals can eventually recover without antibiotics.29

**Current Pertussis Infection Rates**

Compared with other respiratory illnesses, the overall number of pertussis cases is low; however, rates are on the rise. Pertussis incidence typically cycles with increased activity every 3 to 4 years30; on average, the overall number of reported pertussis cases in the United States has gradually increased since 1976.31 (Fig. 2). According to the CDC, >21,000 cases were reported in 2010, marking the highest annual incidence since the 1950s. The annual incidence of pertussis has increased three-fold in the United States since 1980.32 Even among groups with high vaccination rates, *B. pertussis* continues to circulate and cause disease.31 Waning of vaccine-induced immunity is an important factor. Waning is seen with both vaccine-induced immunity30 and natural immunity after acute infection. Adults who develop pertussis can transmit the disease to susceptible infants in the household, and these unvaccinated infants are at higher risk of morbidity and mortality from this infection. More than half of infants with pertussis contract the disease from family members, mostly from their mothers, followed by siblings.31

In recent years, infants have been experiencing increases in both infection and complication rates33 and have been at increased risk of requiring hospitalization.32 Infection with pertussis among adults poses a serious threat to infants aged <1 year, as they may be unimmunized or incompletely immunized. The recommended immunization schedule for infants includes 3 doses of diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP); usually, these doses are completed by 6 months of age. Therefore, immunization efforts in parents and siblings are recommended to prevent transmission to young infants in the household.31 In response to this need, the ACIP recently recommended Tdap to pregnant women; this was also endorsed by the Committee on Obstetric Practice of the American College of Obstetricians and Gynecologists.34,35

**Pertussis Vaccination**

Tetanus and diphtheria toxoid vaccines are bacterial toxins that are modified to make them nontoxic; these are combined with acellular pertussis vaccines (Tdap). Acellular vaccines use selected pertussis antigens to induce immunity rather than including the whole cell. Acellular vaccines are considered safer, but are generally more expensive. There are 2 licensed Tdap vaccines for adolescents and adults; 3-component pertussis vaccine combined with diphtheria and tetanus toxoid (BOOSTRIX) or 5-component pertussis vaccine combined with diphtheria and tetanus toxoid (Adacel). Unfortunately, immunity following vaccination wanes over time.

**Current Recommendations for Pertussis Vaccination**

In 2006, the ACIP recommended Tdap for routine use in adolescents and adults. At that time, the ACIP recommended the vaccine could be used in pregnancy but preferred postpartum administration to affect the cocooning strategy described previously. In a modeling study, cocooning was predicted to lead to a 9% to 17% reduction in adult pertussis cases and a decrease of 70%, 65%, and 69% in cases among infants aged 0 to 3 months, 4 to 23 months, and 2 to 4 years, respectively.36 In an updated summary, released in 2008, ACIP recommended postpartum women who have never been vaccinated with Tdap and whose last tetanus-diphtheria vaccine was at least 2 years ago, should receive a single Tdap vaccine before hospital discharge to provide personal protection and reduce the risk for transmitting pertussis to their infants. In addition, pregnant women with urgent indication for tetanus or diphtheria toxoid vaccination should be vaccinated with Tdap immediately to prevent maternal or neonatal disease. However, as immunogenicity studies become available, there has been concern for insufficiently rapid
immune response to protect infants in the first weeks of life. Consequently, the ACIP in June 2011 provided Recommendations for Pregnant Women on Use of Tetanus toxoid, Reduced Diptheria Toxoid, and Acellular Pertussis Vaccine (Tdap), released in August 2011. Those recommendations are reflected as follows:

- **Use of Tdap in pregnant women**
  - Women’s health care providers should implement a Tdap vaccination program for pregnant women who have not received Tdap. Health care providers should give Tdap during pregnancy, preferably during the late second or third trimester. Alternatively, if not administered during pregnancy, Tdap should be given immediately postpartum.

- **Vaccination of adolescents and adults in contact with infants**
  - Adolescents and adults who have or who anticipate having close contact with an infant aged <2 months and who previously have not received Tdap should receive a single dose of Tdap to protect against pertussis. Ideally, these adolescents and adults should receive Tdap at least 2 weeks before close contact with the infant.

- **Pregnant women with unknown or incomplete tetanus vaccination**
  - To ensure protection against maternal and neonatal tetanus, pregnant women who never have been vaccinated against tetanus should receive the series of THREE vaccinations during pregnancy. The recommended schedule is: time of initial vaccine, and 4 weeks later, and then a third at 6–12 months later. A Tdap vaccine should replace 1 dose of Td, preferably during the late second (>20 weeks) or third trimester of pregnancy.

- **Pregnant women due for tetanus booster**
  - If a tetanus and diphtheria booster vaccination is indicated during pregnancy for a woman who has not previously received Tdap (>10 years since Td), then health care providers should administer Tdap during pregnancy, preferably during the late second (>20 weeks) or third trimester of pregnancy.

Although revised guidelines recommend Tdap in pregnancy and safety profiles have been documented, studies examining immunogenicity and outcome of pregnancy for pregnant women who receive Tdap are limited. In one report of 104 mother–infant pairs, 52 mothers received Tdap during pregnancy. Newborns delivered to the immunized mothers had increased levels of antibody. Unfortunately, it is still unclear what level of serologic antibody confers protection from disease. Further, studies of the impact of maternal vaccination on the subsequent immune responses in infants are ongoing.

In summary,

- Influenza infection is a repeated risk, given the evolution of new viral strains resulting from antigenic drift.
- Influenza illness is characterized by the acute onset of fever, malaise, rhinorrhea, sore throat, and headache.
- Because pregnant women are disproportionately affected by influenza, suspected influenza illness should be treated promptly, based on clinical symptoms. Rapid diagnostic tests are not sensitive enough to withhold treatment based on a negative test.
- Influenza vaccination improves maternal and possibly neonatal outcomes and should be administered annually to all pregnant women regardless of gestational age.
- Pertussis infection is on the rise. Although adults may have been vaccinated as children, immunity wanes over time. The most significant burden of mortality from pertussis occurs in infants aged <6 months.
- Pertussis infection can be difficult to diagnose and should be based on clinical history with a low index of suspicion. Early macrolide treatment can reduce contagion and reduce the clinical course.
- As of August 2011, Tdap vaccination is recommended for pregnant women in the late second (>20 weeks) or third trimester who have not previously received Tdap. If not given during pregnancy, Tdap should be given postpartum.

**REFERENCES**


