Vaccination during pregnancy: first line of defense for expecting mothers and vulnerable young infants

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Purpose of review
Maternal vaccination is a well-tolerated and effective way to protect mothers, their developing fetuses, and their young infants from infectious diseases. Although influenza vaccine and diphtheria, tetanus, and acellular pertussis (Tdap) vaccine are recommended for all pregnant women, uptake rates in the United States remain low. This review will focus on the rationale, scientific evidence, and perceptions of vaccination during pregnancy.

Recent findings
Recent studies show that administration of influenza and Tdap vaccines during pregnancy is well tolerated and provides protection to the pregnant woman, her fetus, and young infant. Studies have shown that many pregnant women look to their obstetricians to guide their prenatal care. A strong provider recommendation remains the greatest impetus to increase vaccine uptake. Both healthcare providers and expectant mothers should continue to be educated on the importance and safety of the influenza and Tdap vaccines during pregnancy.

Summary
Providers play a central role in advising patients and their families about the importance of maternal vaccination. The strong recommendation of providers and the availability of maternal vaccines in OB/GYN offices are keys to improve vaccine uptake. Attention must be paid to further development of intervention techniques that address unique barriers such as vaccine cost, storage concerns, and misinformation about vaccine safety.

Keywords
inactivated vaccine, influenza, maternal immunization, pertussis, Tdap vaccine

INTRODUCTION

Maternal immunization can protect the pregnant woman, her fetus, and the vulnerable young infant after birth from serious and life-threatening infectious diseases. Maternal and neonatal tetanus, for example, has been nearly eradicated through successful global efforts to establish maternal immunization programs [1]. This initiative, backed by the WHO and UNICEF, began in 1989 after nearly 790 000 newborn tetanus-related deaths occurred during the prior year [1]. In 2013, the WHO estimated that 49 000 newborns died from neonatal tetanus, a 94% reduction from the late 1980s [1]. The success of this vaccine program demonstrates that maternal immunization can have a widespread impact on decreasing the morbidity and mortality of infectious diseases.

Although maternal and neonatal tetanus is no longer of concern in the United States, [2] lack of maternal vaccination uptake against influenza and pertussis continues to be a major barrier to optimal maternal and infant health. Influenza poses serious risks for expectant mothers and their young infants, for whom no influenza vaccine is licensed until age 6 months of age [3▪▪]. Despite a recommendation for influenza vaccination during pregnancy by the US Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC), rates are estimated at 46.6% for the 2016–2017 season, a modest increase from 40.2% during the 2015–2016 season [4]. Beginning in 2011, the ACIP also began recommending diphtheria, tetanus, and acellular pertussis (Tdap) vaccine during each pregnancy. In 2015, the estimated uptake of Tdap remained low at 42%, but had increased from 27% reported in 2014 [5].

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KEY POINTS

- The ACIP and ACOG recommend influenza vaccine for all pregnant women during the influenza season.
- The ACIP and ACOG also recommend that all pregnant women receive diphtheria, tetanus, and acellular pertussis vaccine between 27 and 36 weeks of gestation.
- For providers, cost and storage of these vaccines pose challenges to increasing vaccination uptake.
- For expectant mothers and families, concerns about safety of vaccination during pregnancy and ease of access are key barriers to uptake.

This review will begin by introducing the current recommendations for maternal immunization to protect against influenza and pertussis, including the supporting safety studies and biological mechanisms of action. We will then discuss recent data showing the effectiveness of influenza and pertussis immunization during pregnancy, provider perceptions of maternal immunization, reasons for vaccine hesitancy and refusal, and identified barriers to increasing maternal vaccine uptake. Finally, we will identify next steps and areas for future study, including an overview of the development of vaccines against respiratory syncytial virus (RSV) and Group B streptococcus (GBS).

RECOMMENDATIONS AND PRINCIPLES OF MATERNAL IMMUNIZATION

The ACIP recommends influenza vaccine for all women who are pregnant during the influenza season [6]. Pregnant women and young infants have been identified to be at high risk for illness and complications from influenza [6]. There is some evidence that the increased susceptibility to influenza in pregnant women may be because of physiological changes, such as alternated cell-mediated immunity, that occur naturally during pregnancy [3▪▪,5]. Expectant mothers with influenza have an increased risk of premature labor and delivery, contributing to a greater risk of infant morbidity and mortality [7]. Increased infection severity, morbidity, and mortality were reported during the 2009 (H1N1) pandemic in both pregnant and postpartum women, highlighting the vulnerability of this population as compared with women who are not pregnant [8]. Vaccinating expectant mothers offers protection to the infant through the transfer of maternal antibodies via the placenta. It is critical to passively protect the young infant although the influenza vaccine is licensed for children beginning at 6 months of age [6]. Therefore, the first 6 months of life represents a period in which the infant cannot be protected from influenza by direct immunization.

Vaccination of the expectant mother protects both the pregnant woman and her young baby. Infant protection from influenza can be further enhanced by vaccinating all family members and caretakers of young infants. Preferably, individuals should be vaccinated before the start of influenza season to allow adequate time for protection to develop from the vaccination. Individuals should ideally be vaccinated by the end of October, if possible, although it usually takes a minimum of 2 weeks for a protective antibody response to develop. Additionally, the onset of each influenza season is unpredictable. An unimmunized person may be vaccinated at any time throughout the influenza season although multiple outbreaks of influenza can occur within a community during the same influenza season. Inactivated influenza vaccine can be administered at any time during pregnancy [8]. Live, attenuated influenza vaccine is not recommended during pregnancy [6].

Pertussis cases have risen alarmingly in recent years. In 2015, the rate of pertussis infections for infants less than 6 months of age was 99 per 100 000 live births [9]. Mortality slightly decreased in comparison with the two prior years, 2013 and 2014; three infants under 1 year of age died because of pertussis infection in 2015 [9]. Beginning in 2000, annual surveillance reports have found that approximately 80% of pertussis hospitalizations and 90% of pertussis deaths occur in infants less than 1 year of age [10]. Peaks in reported cases of disease occur approximately every 3–5 years, with the last substantial peak occurring in 2012 (41 000 cases, 18 deaths along all age groups) [9]. Many infants acquire pertussis from family members, often from the mother (20.6%) and commonly from siblings 35.5% [11]. In 2006, the ACIP released a recommendation which was supported by the American College of Obstetricians and Gynecologists (ACOG) that all postpartum mothers and close family contacts should receive the Tdap vaccine [11,12] Although infants cannot begin to be vaccinated against pertussis until 2 months of age, vaccinating the mother and family contacts was thought to provide a secondary effect of cocooning the infant against possible illness. However, there are numerous barriers to implementing this cocooning strategy, including cost of vaccination, lack of opportunity to engage family members, and disruption of the patient-centered medical home [11,12]. Although this practice is encouraged, cocooning has not been documented to provide direct protection to the

vulnerable infant. To provide the highest level of protection, the ACIP voted in 2012 to recommend that all pregnant women receive the Tdap vaccine between 27 and 36 weeks of gestation during each pregnancy [12]. This recommendation is supported by the ACOG [8]. Although there is a lack of high-quality studies about the safety of tetanus-toxoid-containing vaccines, these vaccines have been used for a considerable amount of time in many countries and have not been shown to pose risk to pregnant women or their fetuses [13]. At the ACIP's October 2016 meeting, the committee indicated that there are data, suggesting that immunization earlier in the 27–36 weeks of gestation timeframe maximizes passive antibody transfer to the infant [14].

Maternal immunization effectively protects both the mother and her infant from infectious diseases. Once vaccinated, maternal immunoglobulin G (IgG) is passed to the infant via the placenta, predominantly during the third trimester [15]. The mother may transfer IgA to the infant via colostrum during breastfeeding, but this offers little direct protection against infectious diseases because these antibodies are limited to the gastrointestinal tract of the infant [16]. Although the highest placental transfer occurs in the final 4 months of pregnancy, maternal IgG has been detected as early as 13 weeks of gestation [16]. Following Tdap immunization, IgG, as well as IgA, antibodies against pertussis toxoid increased markedly by days 5–7, reached their peak by day 14, and then decreased through day 28 [17]. In a randomized, double-blind, placebo-controlled, clinical trial, Munoz *et al.* [18] found that maternal pertussis antibody levels at delivery were markedly higher for women who had received the vaccine during pregnancy than those who had received it postpartum, 51 EU/ml as compared with 9.1 EU/ml. Additionally, infants of mothers who had received Tdap antepartum had a higher concentration of pertussis antibodies at birth (68.8 EU/ml) as compared with (14.3 EU/ml) infants whose mothers received Tdap postpartum. These infants also had a higher concentration of pertussis antibodies at 2 months of age (20.6 EU/ml) as compared with (5.3 EU/ml) infants whose mothers received Tdap postpartum [18]. Healy *et al.* [19] investigated the timing of pertussis vaccination by analyzing 105 maternal-umbilical cord serum pairs. Comparing pertussis toxin levels in the infant cords (17.3 EU/ml) with their mothers at time of delivery (10.5 EU/ml), higher levels of antibodies in the infants demonstrate active transport via the placenta. Additionally, mothers vaccinated later in their third trimester had the highest levels of pertussis toxin levels at delivery and the most efficient antibody transfer to their infants [19]. These findings support the ACIP's recommendation of an optimal vaccination window between 27 and 36 weeks of gestation.

VACCINE EFFECTIVENESS AND ADDITIONAL CONSIDERATIONS FOR MATERNAL VACCINATION

In recommending vaccination for pregnant women, vaccine safety and effectiveness must be closely analyzed. All policies seek to ensure that any potential risk is greatly outweighed by the benefits of maternal vaccination [9,20▪]. In the Munoz *et al.* [18] study of 48 pregnant women who received Tdap or a placebo antepartum, the most commonly reported event was site injection pain by 78% of women who received Tdap antepartum compared with 13.3% of placebo recipients. All infants were live born and no cases of pertussis were reported in either mothers or infants [18]. There were no significant differences noted in infants' gestational ages and developmental markers between study groups. Although the small sample size poses limitations on generalizability, this study shows potential benefits to maternal vaccination in protecting infants from pertussis based on antibody levels achieved in the infants. In one large observational study ($n = 26{,}684$) of laboratory-confirmed cases of pertussis completed in England between October 1, 2012 and September 30, 2013, vaccine effectiveness was found to be 90% [95% confidence interval (CI) 82–95] when restricted to infants less than 2 months of age [21]. A retrospective cohort study conducted in the United States examined infants who had pertussis between 2011 and 2015 [22]. Infants of mothers who had received Tdap intrapartum had lower hospitalization rates with an adjusted vaccine effectiveness for preventing hospitalization of 58% (95% CI 15–18%) [22]. None of the infants with pertussis who were born to mothers vaccinated intrapartum required intubation or died, demonstrating that Tdap maternal vaccination during pregnancy reduces the severity of disease. One limitation to this study was that vaccination during pregnancy was not limited to the presumed optimal window of 27–36 weeks of gestation. However, higher antibody titers were observed in infants whose mothers had been vaccinated in the third trimester [22]. The diverse study population and large data set are surely encouraging in demonstrating the importance of antepartum Tdap vaccination.

The ACIP has identified pregnant women as a population to target for influenza vaccination [6]. Vaccine effectiveness has been shown to be favorable for both infants and mothers. However, although influenza virus antigens frequently drift or sometimes shift, there are limitations on the development of a highly effective vaccine each year.

Thompson *et al.* [23] conducted a study in California and Oregon, during the 2010–2011 and 2011–2012 influenza seasons. Effectiveness using influenza-negative controls was found to be 44% (95% CI, 5–67%) [23] as compared with results in a meta-analysis in 2012, in which the pooled efficiency of 10 randomized control trials for trivalent influenza vaccine was 59% (95% CI 51–67) in adults aged 18–65 years [24]. A Zamen *et al.* [25] study conducted in Bangladesh randomly assigned 340 mothers to receive either the influenza vaccine or pneumococcal polysaccharide vaccine (control) during the third trimester. Mothers who received the influenza vaccine were less likely to have respiratory illness with fever, and among the 159 infants whose mothers received the influenza vaccine antepartum, 6 had laboratory-confirmed influenza. Compared with 16 who had laboratory-confirmed influenza among the 157 infants in the control group, vaccine effectiveness against influenza was 63% (95% CI 5–85) in this study [25]. In Mali, a prospective, active-controlled, observer blind, randomized Phase IV study vaccinated women in their third trimester with either trivalent influenza vaccine ($n = 2108$) or meningococcal vaccine ($n = 2041$) [26]. Among those infants followed until 6 months of age, there were 131 (2%) cases of laboratory-confirmed influenza, only 52 of which were in the influenza vaccine group [26]. Overall vaccine effectiveness in this intention to treat group started off high, 67.9% in the first 4 months, and then subsequently fell. Overall vaccine effectiveness in infants whose mother received the vaccine was 33.1% at 6 months of age and vaccine effectiveness in vaccinated mothers was 70.3% [26]. In a retrospective cohort study of nearly 150 000 infants, Baxter *et al.* [27▪▪] found that maternal immunization offered additional protection to infants following DTaP administration through the first year of life (DTaP is the diphtheria, tetanus, and acellular pertussis vaccine licensed for children less than seven years of age). Effectiveness in preventing pertussis in the first 2 months of life was found to be 91% [27▪▪]. After adjusting for protection provided by the three-dose DTaP series, vaccine effectiveness of the maternal Tdap vaccine was found to be 69% [27▪▪].

A potential drawback of maternal vaccination and the subsequent transfer of maternal antibodies to the fetus is the potential inhibition of the infant immune response following the infant's primary series. The evidence is mixed, but generally shows no significant negative effect of intrapartum maternal immunization [15]. Munoz *et al.* [15,18] show that titers of passively transferred antipertussis antibodies wane quickly and that the DTaP vaccine dose received at 2 months of age results in a robust and appropriate immune response. One month following the final DTaP dose received at 1 year of age, pertussis antibody concentrations were not significantly different between infants of mothers immunized during pregnancy and infants whose mothers were immunized postpartum (80.1 EU/ml compared with 83.9 EU/ml, respectively) [18]. Baxter *et al.* [17] also found no interference between maternal Tdap and infant DTaP-related protection in their large California cohort studied. Another study conducted by Hardy-Fairbanks *et al.* [28] found that infants born to antepartum Tdap-vaccinated mothers had a reduced response to the primary DTaP series. However, it is important to note that differences with controls diminished after the booster, and the study was limited by the small sample size of the Tdap during pregnancy group ($n = 16$) [28]. Although some reports do show a diminished response to DTaP following maternal intrapartum Tdap vaccination, the majority do not corroborate such an interaction. Additionally, if an interaction is present, it appears to be minimal, not clinically significant, and resolves itself with completion of the DTaP booster. Ultimately, the goal of maternal immunization is to protect infants during the time when they are the most vulnerable to infection [29]. Although infants less than 3 months of age have the highest morbidity and mortality from pertussis, ACOG has noted that the benefits of maternal vaccination greatly outweigh unproven concerns [8,30]. ACIP is continuing to monitor established safety systems for adverse events associated with receipt of Tdap during each pregnancy. Extensive review of available data has revealed only local adverse effects for multiple Tdap vaccines given during repeat pregnancies; with the most commonly reported event being pain at the injection site [12]. However, although these studies included a relatively small number of subjects, there is still a need for further research and surveillance of women who receive the Tdap vaccine during pregnancy, particularly subsequent doses spaced closely together, to determine the risk of severe, albeit rare, adverse events.

PERCEPTIONS OF MATERNAL IMMUNIZATION

Several studies have shown that provider recommendation is associated with a higher likelihood of vaccine uptake. In a study conducted among obstetricians in New York, it was found that 92% of surveyed providers ($n = 133$) knew about the ACIP Tdap vaccine recommendation [31]. However, 20% of providers do not recommend the vaccine to all their patients. Safety of maternal vaccination was found to be of concern with 5% of obstetricians for

influenza vaccine and with 11% of obstetricians for the Tdap vaccine [32]. These data are of interest although there has been extensive research proving the safety of both vaccines during pregnancy and points to the need for continued education. Additionally, many providers noted that they did not recommend the Tdap vaccine in the office because they believed it would be offered on the postpartum floor [32]. Another identified barrier to vaccine uptake was the lack of vaccine supply at the obstetrician's office. In the same survey of New York providers, only 62% had the Tdap vaccine available in their offices [31]. Obstetricians support a standing order on postpartum floors for the vaccine as a way to increase vaccine reception and reduce coordination logistics [33]. Cost and lack of reimbursement were commonly cited as barriers to offering either the influenza or Tdap vaccines on site in the ambulatory setting [32,33,34].

Obstetricians are perceived by pregnant women to be the most trusted physicians [34]. Their lack of recommendation represents a missed opportunity to educate families about the importance of vaccination [33]. Additionally, provider recommendation may also influence how the mother perceives vaccines as a parent [33]. Early discussion and recommendation of vaccines may serve to combat parental vaccine hesitancy and refusal later in the child's life. Although several surveys presented to providers focused on whether the vaccine was recommended at all, there has also been recent research into how the type of recommendation made may influence vaccine acceptance. In a study of parental vaccine acceptance, it was found that participatory formats in which receiving the vaccine was presented as a question ('Would you like to receive this shot today?') were more heavily associated with vaccine hesitancy and refusal [34]. However, when providers presented the vaccine in a presumptive manner ('You are to receive this vaccine today'), there was greater vaccine uptake [34]. The differences in provider presentation of vaccines to pregnant women may be an interesting area of further research, particularly given how highly obstetricians' recommendations have been noted in several studies [18,32,33,35].

Provider perception, knowledge, and recommendation of vaccination play a large role in the success of maternal immunization programs. One cluster-randomized trial analyzed the effectiveness of a package of interventions (e.g., vaccine champion, provider to patient talking points, educational brochures, and an educational phone application) and found that provider recommendation was most strongly correlated with vaccine uptake [35]. However, increases in influenza or Tdap vaccine coverage were not significant, pointing to the need for further development of interventions which target specific barriers to maternal immunization. A review article found that many women are not aware of the risk of influenza disease during pregnancy and may therefore perceive the vaccine against influenza as unnecessary [36]. Additionally, there is substantial concern among women that vaccination during pregnancy is dangerous to the health of the developing fetus [31]. Educational materials in conjunction with provider recommendation may serve to lessen some of these concerns [37]. Education materials should be targeted, focusing on vaccine safety, efficiency, and the benefit of protecting both the vulnerable infant and mother from illness [38]. A novel study regarding text message reminders sent to pregnant women found that the informational messages did not increase uptake of the influenza vaccine [39▪]. This illustrates that future work must determine the best manner to target this population in order to increase acceptance of maternal vaccines during pregnancy.

Interestingly, many women regarded influenza and pertussis as concerns for pregnant women, 82% and 81%, respectively. Not surprisingly then, only 34% and 44% of women received the influenza and pertussis vaccines, respectively [38]. These survey results show that although there has been widespread coverage of influenza and pertussis following recent outbreaks, safety of the vaccines continues to be of primary concern of expectant mothers. It is also important to note that the ACIP continues to recommend cocooning as a method to protect infants from pertussis. If mothers remain reluctant to receiving the vaccine during pregnancy, it is beneficial to the health of the infant to recommend that family members are vaccinated as soon as possible and that the mother receive the vaccine postpartum [39▪]. Family members continue to be difficult to reach although vaccinating these individuals introduces challenges of cost and disturbing the integrity of the medical home. There must be continued effort to examine the best timing and locations to educate pregnant women and their families about the importance of being vaccinated against these preventable diseases.

NEXT STEPS IN MATERNAL VACCINATION

Several other maternal vaccines are currently in late stages of investigation. One of interest is the vaccine to protect against the RSV which causes 33.8 million lower respiratory tract infections (LRTIs) for children under the age of 5 across the world annually [40]. Data suggest that globally, the annual mortality rate is twice as great for children less than 1 year of age and RSV accounts for approximately

3.4 million hospitalizations because of LRTI worldwide [40–41]. A study conducted in the United States between October 2000 and March 2005 found that the hospitalization rate for infants less than 2 months of age was 17.9 per 1000 children [42]. The highest hospitalization rate, 25.9 per 1000 children, was among infants less than 1 month of age [42]. This demonstrates the high burden of disease among young infants and provides an impetus for the swift development of a maternal vaccine [42]. Numerous studies, some as late Phase II clinical trials, are investigating the possibility of maternal vaccination to protect young infants from RSV. A vaccine will be available in the next 5–10 years, according to WHO estimates [43].

Another antigen of interest is GBS, which causes severe disease in newborns, including sepsis, pneumonia, and meningitis [44]. Prevention methods currently rely on screening mothers between 35 and 37 weeks of gestation and treating women found to be colonized with an antibiotic intravenously during labor [44]. In one retrospective study conducted in Wisconsin, colonization rate was found to be 22.3% for 99 305 women, where rate of infant death following hospitalization was 0.57% ($n = 558$) [45]. Nanduri *et al.* [46] reviewed GBS cases identified by Active Bacterial Core surveillance and found that despite use of intrapartum antibiotic prophylaxis although the 1990s, early-onset disease caused by GBS infection has plateaued at 0.26 per 1000 live births and late-onset disease by GBS infection remains high at 0.3 per 1000 live births. Assuming vaccine effectiveness of 80%, a vaccine could prevent approximately 600 cases of early-onset disease and 580 cases of late-onset disease [46]. GBS vaccines are in Phase II of investigation; a study conducted in South Africa by Madhi *et al.* [47] found that a trial GBS maternal vaccine was well tolerated and resulted in a GBS-specific antibody response in both mothers and their infant. However, substantial regulatory and licensing barriers remain in the development of a GBS vaccine [48].

CONCLUSION

Pregnant women, their fetuses, and their young infants are at increased vulnerability to dangerous infections such as influenza and pertussis. Both the ACIP and ACOG recommend the vaccination of expectant mothers against these two pathogens with the intention that this practice will protect infants who are too young to receive the influenza and Tdap vaccines themselves. Evidence supports the safety and effectiveness of influenza and Tdap vaccines in pregnant women.

Much work needs to be done to implement these maternal immunization recommendations. Future studies must further examine provider perception and patient hesitancy. Special attention must also be paid to the barriers of maternal vaccination, including, but not limited to, patient cost, provider reimbursement, and storage of the vaccine in ambulatory settings. Additionally, efforts of continued education for both providers and patients must be a central part of any maternal immunization program. Providers must continue to strongly recommend and support Tdap and influenza vaccine administration to expectant mothers, in accordance with current ACIP recommendations. Ongoing efforts may bring about additional vaccines for use in pregnant women to reduce the risk of other serious infections in them and/or their offspring.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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■■ This review offers a detailed overview of key topics in maternal immunization. Importantly, the mechanism of action for maternal vaccination and increased susceptibility of pregnant women are discussed. The bulk of the paper outlines current recommendations for both routine and special circumstance vaccine administration. Both influenza vaccine and Tdap vaccine are evaluated in more detail. Lastly, Omer introduces some vaccines currently under development. Table 1 provides an overview of all vaccine recommendations for pregnant women in the United States.

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In a retrospective cohort study, the authors analyzed the effectiveness of Tdap maternal vaccination for protecting newborns in the first year of life. This study also importantly highlights whether any interaction occurs between the Tdap vaccination received by the mother during pregnancy and the infant's DTaP series. The study population consisted of 148 891 infants, 45.8% whose mothers received Tdap during pregnancy. Of 17 confirmed cases of pertussis, only 1 case occurred in an infant whose mother had been vaccinated antepartum, more than 7 days prior to birth. Vaccine effectiveness because of maternal Tdap vaccination was an estimated 91.4% for the first 2 months of life. When adjusting for DTaP vaccination, vaccine effectiveness of the maternal Tdap vaccine was found to be 69.0% for the first year of life. Importantly, the high vaccine effectiveness through one year of life shows no evidence of interference between the maternal Tdap vaccine and the DTap series.

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