

REVIEW ARTICLE

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Maternal Immunization

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VACCINES HAVE BEEN ONE OF THE MOST USEFUL TOOLS FOR ACHIEVING substantial reductions in childhood mortality. However, progress in reducing deaths has been slower for infants too young to be vaccinated than for infants and children old enough to receive vaccines.¹

Immunization schedules start when infants are 2 months of age in the United States and many other high- and middle-income countries and 6 weeks of age in most low-income countries. The primary immunization schedule is not complete until infants are 6 months of age in most high- and middle-income countries and 14 weeks of age in most low-income countries. Therefore, most childhood vaccines do not start providing adequate protection until the infant is several months old. This inability to use vaccines to prevent infections in neonates and young infants leaves an immunity gap that results in a higher proportion of infection-related hospitalizations and deaths in these age groups than in older children.

This vulnerability of infants who are too young to be vaccinated can be addressed by means of maternal vaccination. Moreover, several infections, such as influenza and hepatitis E, are considered to be associated with increased morbidity and mortality during pregnancy. Maternal vaccines, given their potential effect on maternal and infant morbidity and mortality, are the next frontier in vaccinology. This article synthesizes the evidence for current maternal immunization recommendations, reviews new developments in this rapidly evolving field, and outlines critical areas for future research that will provide a framework for a comprehensive maternal immunization platform.

PREGNANCY AS AN IMMUNOLOGICALLY DYNAMIC STATE

Sex hormones modify immune responses. During the course of pregnancy, changing levels of sex hormones induce variable immune responses (Fig. 1). Increases in estradiol levels during pregnancy are associated with relatively higher type 2 helper T-cell (Th2) responses and diminished type 1 helper T-cell (Th1) responses and therefore contribute to a Th1-to-Th2 shift in pregnancy.^{2,4} Moreover, increasing progesterone levels during pregnancy are associated with a reduction in immune responses and an alteration of the Th1–Th2 balance.^{5,6} Other components of the immune response, such as phagocytic activity, alpha-defensin expression, and the numbers of neutrophils, monocytes, and dendritic cells, are maintained and may even increase during the second and third trimesters.⁶

The alteration in cell-mediated immunity helps explain suboptimal responses to certain viral infections, such as influenza, that require robust cell-mediated immunity to suppress viral replication.⁷ However, other parts of the immune system are maintained and, in some cases, enhanced, probably accounting for the fact that pregnancy is not a generalized state of immunosuppression.

Evidence regarding the immunogenicity of vaccines administered to pregnant

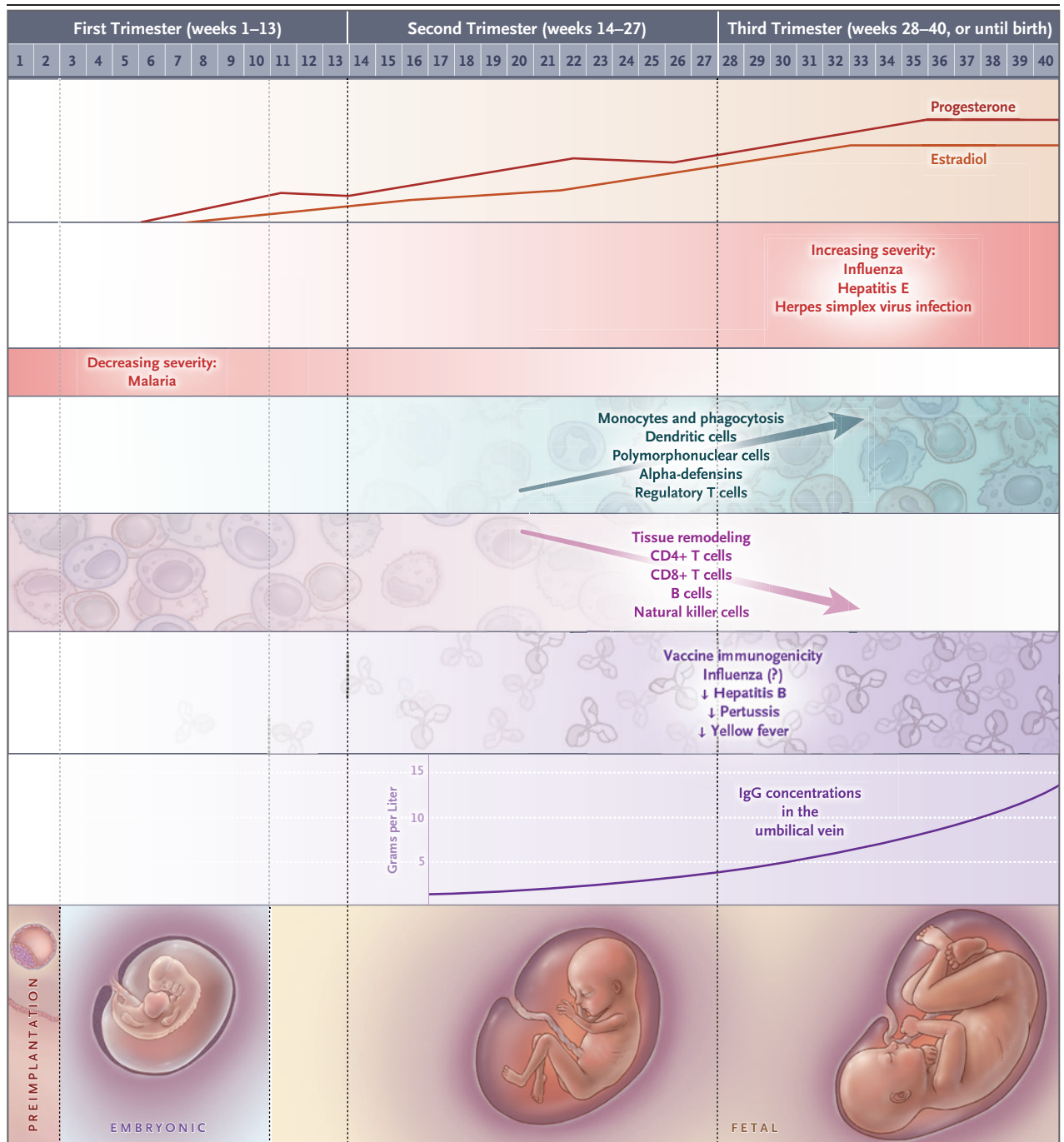


Figure 1. Vaccine and Immune Responses during the Course of Pregnancy.

Adapted from Kourtis et al.² and Malek et al.³

women, as compared with nonpregnant women, is mixed. In some studies, mainly involving inactivated influenza vaccine, equivalent responses were observed in pregnant and in nonpregnant women.⁸⁻¹⁰ Studies of vaccination against hepatis

tis B,¹¹ influenza,^{12,13} pertussis,¹⁴ and yellow fever¹⁵ showed lower immunogenicity in pregnant women than in nonpregnant women. Notably, studies that showed the reduction in immunogenicity did not provide evidence of a decrease in the

clinical effectiveness of vaccination during pregnancy.¹²⁻¹⁶

EVIDENCE FOR CURRENT MATERNAL IMMUNIZATION RECOMMENDATIONS

In the United States, the recommendations for maternal immunization include the inactivated influenza vaccine and the combined tetanus–diphtheria–acellular pertussis (Tdap) vaccine. In some other countries, pregnant women also receive hepatitis B vaccine, hepatitis E vaccine, or both. Table 1 lists vaccines and current recommendations for their administration during pregnancy.

INFLUENZA VACCINE

Influenza vaccine has been recommended for pregnant women in the United States since the 1960s.²⁰ Currently, influenza vaccine is now recommended for all pregnant women (during each pregnancy). The vaccine can be administered in any trimester of pregnancy. Many other developed and middle-income countries now have recommendations for maternal influenza immunization. Similarly, in 2012, the World Health Organization's Strategic Advisory Group of Experts on Immunization recommended that countries considering the initiation or expansion of seasonal influenza vaccination programs give the highest priority to pregnant women.²¹ Despite this recommendation, few low-income countries regularly vaccinate pregnant women against influenza.

The justification for vaccinating pregnant women includes evidence, mainly from observational studies, suggesting that influenza results in more severe outcomes among pregnant women than among nonpregnant women. The evidence of more severe maternal and fetal outcomes after influenza is more consistent for pandemics²²⁻²⁶; nevertheless, a substantial burden of illness among pregnant women is attributable to seasonal influenza.²⁷⁻³² Similarly, infants under 6 months of age have the highest burden of childhood complications and death associated with influenza.³³ However, no efficacious vaccines are licensed and available for infants younger than 6 months of age.³⁴

Influenza vaccines are efficacious against influenza-like illness and laboratory-confirmed influenza in pregnant women and their in-

fants.³⁵ Four randomized, controlled trials, conducted in South Africa, Mali, Nepal, and Bangladesh, have evaluated the efficacy of inactivated influenza vaccine administered during pregnancy^{36,37} against laboratory-confirmed maternal and infant infection. In these trials, the efficacy in infants ranged from 30% in Nepal to 63% in Bangladesh (Fig. 2).^{18,37-39}

Given the reported association between influenza during pregnancy and adverse birth outcomes, the potential protective effects of maternal influenza vaccination against adverse birth outcomes (e.g., low birth weight) have been explored. The evidence from clinical trials is characterized by subtle shades of meaning that require some interpretation. For example, in the Bangladeshi and Nepalese trials, maternal influenza immunization was associated with protection against low birth weight,^{39,40} whereas the South African and Malian trials did not show such an association. The Nepalese trial showed a 15% reduction in the incidence of low birth weight among newborns of vaccinated mothers as compared with newborns of unvaccinated mothers.³⁹ This difference translated into a mean birth weight that was 43 g higher in newborns of the vaccinated mothers than in newborns of the women in the control group.³⁹ Similarly, in the Bangladeshi trial, the mean birth weight was 193 g higher in the maternal-vaccination group than in the control group during the period of influenza virus circulation.⁴⁰

A few factors should be considered in comparing the results of the four trials. First, whereas all four trials were of high quality, the Nepalese trial was the only one that included a birth outcome (low birth weight) as one of the primary outcomes. Therefore, unlike the other trials, the Nepalese trial was specifically powered to detect a difference in low birth weight between the study groups, reducing the likelihood of a type II error.

Second, the women in the Malian, Bangladeshi, and South African trials were vaccinated in the third trimester, whereas the women in the Nepalese trial received the vaccine between 17 weeks and 34 weeks of gestation.^{36,37} Early vaccination may have provided a longer period to influence fetal growth and weight gain. Moreover, assessment of gestational age can be inaccurate for women presenting late in pregnancy.

Table 1. Overview of Vaccine Recommendations for Pregnant Women in the United States.*

Vaccine and Type	Category	Recommendation for Pregnant Women	Comments and Details
Anthrax, inactivated	Travel and other	May be used in women with high risk of exposure; not recommended for those with low risk of exposure	Generally, inactivated vaccines are considered safe during pregnancy, although limited data from women vaccinated in the U.S. military are of potential concern. The Department of Defense exempts pregnant women from anthrax immunization, but some women inadvertently receive the vaccine. In a study of approximately 115,000 live births to military women, the odds of birth defects were 20% higher for newborns of women vaccinated during pregnancy than for newborns of women who had never been vaccinated. If exposed to anthrax, pregnant women should receive the vaccine and 60 days of antimicrobial therapy.
BCG, live	Travel and other	Contraindicated	Although adverse effects have not been associated with BCG vaccination in pregnant women, it is not recommended during pregnancy, primarily because of theoretical risks associated with live vaccines. Further studies are needed to prove safety before BCG vaccine is used in pregnant women.
HAV, inactivated	Routine	Recommended for specific indications	Recommended for pregnant women who have a history of injection or noninjection illicit drug use, are working with HAV-infected primates, are working with HAV in a research laboratory, have chronic liver disease, receive clotting factor concentrates, or are traveling to or working in countries with high or intermediate endemicity of hepatitis A.
HBV, recombinant	Routine	Recommended in some circumstances	A randomized, controlled trial showed seroconversion rates of 92 to 94% among pregnant women. Older age, obesity, and tobacco smoking have been associated with diminished HBV vaccine responses in pregnancy. Data on vaccine safety during pregnancy, although limited, do not suggest any concerns. Pregnant women who have had an HBsAg-positive sex partner, have had more than one sex partner during the previous 6 mo, have been evaluated or treated for an STD, or are recent or current injection-drug users should receive the HBV vaccine. The recommended schedule is 0, 1, and 6 mo, but an accelerated schedule is possible during pregnancy.
HPV, inactivated	Routine	Not recommended	If a woman is found to be pregnant during the administration of an HPV series, the remaining doses should be delayed until after pregnancy is completed. Although there are limited data for HPV vaccination in pregnancy, the data from vaccine trials and passive surveillance sources such as pregnancy registries and the CDC- and FDA-maintained VAERS have not shown any unexpected patterns in maternal or newborn outcomes of HPV vaccination during pregnancy. ¹⁷
Influenza virus	Routine	Recommended	The inactivated vaccine is recommended for all women who are or will be pregnant during influenza season.
Live, attenuated	Routine	Contraindicated	Because of theoretical risks of fetal infection associated with live vaccines, the live, attenuated vaccine is contraindicated during pregnancy. However, no worrisome patterns regarding adverse birth outcomes have been reported in VAERS.
Japanese encephalitis virus, inactivated	Travel and other	Inadequate data for specific recommendation	There are reports of adverse fetal outcomes after wild-type Japanese encephalitis. However, given the rarity of infection even in areas where the disease is endemic and the relatively high risk of adverse events associated with vaccination during pregnancy, caution should be exercised when considering the use of Japanese encephalitis vaccination in pregnant women. Vaccination should usually be deferred because of the theoretical risk to the fetus. However, a pregnant woman traveling to an area where there is a high risk of exposure to Japanese encephalitis should be vaccinated, assuming the benefits outweigh the risks.

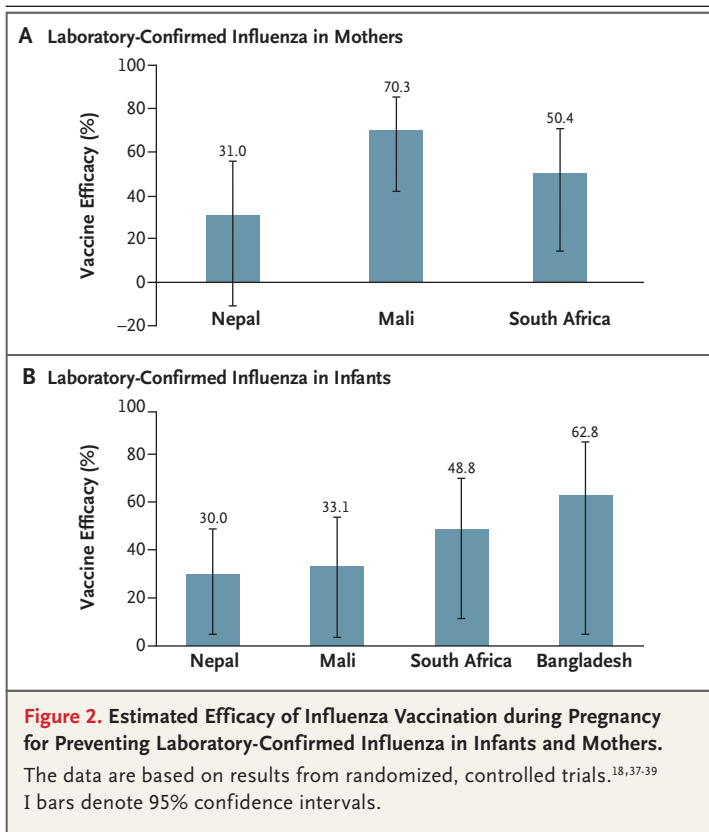
Table 1. (Continued.)

Vaccine and Type	Category	Recommendation for Pregnant Women	Comments and Details
Meningococcal, inactivated	Routine	Serotype ACWY conjugate vaccine may be used in the case of a specific indication; the decision to administer the serotype B vaccine should be based on a risk–benefit assessment for the patient	In the only randomized, controlled trial of maternal meningococcal vaccination, pregnant women in Mali were randomly assigned to receive either serotype ACWY conjugate vaccine or influenza virus vaccine. Although the efficacy or immunogenicity results for the ACWY conjugate vaccine have not been published yet, there were no safety signals in this trial. ¹⁸
MMR, live	Routine	Contraindicated	Because of theoretical risks associated with live, attenuated vaccine, pregnant women or those planning to become pregnant should not receive the MMR vaccine. If the vaccine is inadvertently given to a pregnant woman, she should be informed of the theoretical risks to the fetus. However, receipt of the vaccine is not an indication for termination of pregnancy.
Pneumococcal conjugate (PCV13), inactivated	Routine	Inadequate data for specific recommendation	No published data or recommendations concerning this vaccine seem to exist. However, given the importance of preventing pneumococcal disease in infants too young to be vaccinated, a phase 3 trial of PCV13 is being conducted among Gambian women.
Poliovirus, inactivated	Routine	May be used if needed	This vaccine should not be routinely administered during pregnancy, primarily because of theoretical concerns, since there has been no demonstrated public health reason for maternal immunization. However, if a woman is at increased risk for exposure (e.g., because of travel to an area where the disease is endemic or possible exposure in a clinical or laboratory setting), she may be vaccinated after consultation with her health care provider. No adverse vaccine effects have been observed in pregnant women or their fetuses.
Pneumococcal polysaccharide (PPSV23), inactivated	Routine	Inadequate data for specific recommendation	Although there are insufficient data for a specific recommendation for pregnant women, PPSV23 has been used in the second and third trimesters with no evidence of increased risk. A Cochrane review of randomized, controlled trials determined that there was insufficient evidence that maternal pneumococcal vaccination reduces the risk of infant pneumococcal infection. ¹⁹
Rabies virus, inactivated	Travel and other	May be used in cases of exposure or a high risk of exposure	Given that there are severe clinical consequences of inadequately managed rabies infection, the benefits of administering postexposure rabies vaccine in pregnancy outweigh the risks. A few studies have shown no increase in the risk of preterm birth, fetal abnormalities, or spontaneous abortion. If the risk of rabies exposure is high, preexposure vaccination can be considered. Inadvertent exposure to rabies vaccine during pregnancy should not be considered a reason to terminate the pregnancy.
Smallpox, live	Travel and other	Recommended after exposure; contraindicated before exposure	Smallpox is the only human disease that has been eradicated. However, there are concerns regarding intentional reintroduction (e.g., through bioterrorism) and accidental exposure (e.g., in a laboratory). Transfer of the vaccine virus to the fetus is rare but can have severe clinical consequences, including fetal or neonatal death. Therefore, preexposure vaccination is contraindicated for women who are pregnant or are trying to become pregnant. However, postexposure vaccination is recommended because the risk of smallpox to the pregnant woman and her fetus outweighs any risk associated with the vaccine.

Tetanus toxoid, inactivated, reduced diphtheria toxoid, and acellular pertussis	Routine	Recommended	To ensure passive antibody transfer to the infant, the preferred time of vaccination is between 27 and 36 weeks of gestation, although vaccination during any stage of pregnancy is recommended. If a woman does not receive the vaccine during pregnancy, she should receive it immediately after giving birth. Tetanus toxoid has been shown to be safe and very effective in pregnant women. Moreover, neonates are protected against tetanus through antibodies transferred from vaccinated women. [†]
Typhoid, live and inactivated	Travel and other	Inadequate data for specific recommendation	Live vaccines such as Ty21a are contraindicated for pregnant women. In situations with a clear clinical need, inactivated Vi polysaccharide vaccine should be administered.
Varicella, live	Routine	Contraindicated	Varicella vaccine is contraindicated in pregnancy because of the associated risk of varicella-zoster virus transmission to the fetus or newborn. However, the effect of the vaccine virus on fetal outcomes is unknown. Given that the wild-type virus does not substantially affect the fetus and that the vaccine virus is attenuated, the risk to the fetus in case of transfer of the vaccine virus is likely to be low. In most situations, inadvertent vaccination is not a reason to terminate the pregnancy.
Yellow fever, live	Travel and other	May be used if benefit outweighs risk	Yellow fever vaccination is not contraindicated in pregnancy; however, the risks should be carefully considered. If a pregnant woman cannot avoid travel to an area of high risk for yellow fever, the decision about vaccination should be made by considering the risk of yellow fever as compared with the risks associated with the vaccine. If the vaccination risk is judged to be higher than the disease risk, then the woman should receive a medical waiver so that she can be in compliance with travel regulations that require proof of vaccination or exemption on medical grounds.
Zoster, live	Routine	Contraindicated	The target age group for the zoster vaccine (>60 yr) is outside the childbearing years; pregnant women are unlikely to need this vaccine. Because it is a live vaccine, there is little public health or clinical justification for administering the zoster vaccine to pregnant women.

* Additional references for this table are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org. BCG denotes bacille Calmette-Guérin, CDC Centers for Disease Control and Prevention, FDA Food and Drug Administration, HAV hepatitis A virus, HBsAg hepatitis B surface antigen, HBV hepatitis B virus, HPV human papillomavirus, MMR measles-mumps-rubella, STD sexually transmitted disease, VAERS Vaccine Adverse Event Reporting System, and WHO World Health Organization.

† In addition to safe delivery and neonatal care practices, tetanus toxoid has been the mainstay of the WHO's Neonatal Tetanus Elimination Program and, subsequently, the Maternal and Neonatal Tetanus Elimination Program. These programs have contributed to substantially reducing tetanus-associated maternal and neonatal mortality globally.



For example, in the otherwise well-conducted Malian trial, the investigators used the New Ballard Score to assess gestational age but were able to validate Ballard Score–based gestational age with ultrasonography in approximately 13% of the women participating in the study. In this subset, there was a correlation of only 0.4 between ultrasound-based and Ballard Score–based gestational age.¹⁸

Third, the baseline birth weight was lower in the Nepalese study populations than in the South African and Malian study populations.³⁶ Hence, maternal influenza vaccine may be more useful as protection against adverse birth outcomes in vulnerable populations, particularly if it is given late in the second trimester or early in the third trimester.

Influenza infection is associated with an increased risk of subsequent bacterial infection — particularly, pneumococcal infection and disease.⁴¹ In fact, a substantial proportion of deaths during the 1918 influenza pandemic were probably due to *Streptococcus pneumoniae*.⁴² This potential synergy between influenza virus and *S. pneumoniae*

can be leveraged for young infants through maternal influenza immunization. For example, in the Bangladeshi trial, a 2×2 factorial analysis was performed to determine the antenatal efficacy of influenza vaccination in mothers plus pneumococcal conjugate vaccination in their infants in providing protection against respiratory illness during early infancy.⁴³ As compared with the administration of either inactivated influenza vaccine in mothers or pneumococcal conjugate vaccination (7-valent) in infants alone, the combination of maternal and infant vaccination had higher efficacy against respiratory illness with fever and medically attended acute respiratory illness in infants.⁴³ Similarly, in a study conducted in a U.S.-based managed-care organization, the efficacy of pneumococcal conjugate vaccination was higher for protection against otitis media in infants if their mothers had received inactivated influenza vaccine during pregnancy.⁴⁴

VACCINATION TO PREVENT PERTUSSIS

The primary indication for pertussis vaccination during pregnancy, most often administered as the combined Tdap vaccine, is for the prevention of pertussis in young infants, who have a disproportionately high burden of severe pertussis. Since 2012, pertussis vaccination has been recommended in the United States and the United Kingdom for every pregnancy. These recommendations allow for pertussis vaccination in any trimester of pregnancy but with a preference for late pregnancy: a gestational age of 27 to 36 weeks in the United States and 20 to 32 weeks in the United Kingdom.⁴⁵⁻⁴⁷ Other countries, such as Australia, New Zealand, Belgium, Argentina, and Brazil, also recommend pertussis vaccination during pregnancy.

The recommendations to administer Tdap vaccine to pregnant women evolved in response to large national or subnational pertussis outbreaks. In fact, the current recommendations in the United Kingdom are the result of a temporary vaccination program that was subsequently extended.⁴⁷ The genesis of these recommendations has erected ethical barriers to the conduct of phase 3 trials of Tdap vaccination in countries that recommend maternal pertussis vaccination. Hence, most of the data on the effectiveness and safety of maternal pertussis vaccination come from observational studies.

The studies conducted in the United Kingdom

have shown high effectiveness of maternal pertussis vaccination. For example, the effectiveness for preventing pertussis in young infants was 91% (95% confidence interval [CI], 84 to 95) in a study that used the screening method (which involves the use of readily available administrative and surveillance data), and 93% (95% CI, 81 to 97) in a case-control study.^{48,49}

Similarly, the results of studies evaluating the safety of maternal pertussis vaccination have been reassuring overall. A large study conducted in a network of U.S.-based managed-care organizations showed no increase in adverse birth or pregnancy outcomes, with the exception of a 20% higher adjusted rate of a chorioamnionitis diagnosis among women who received Tdap vaccine during pregnancy (6.1%, vs. 5.5% among women who did not receive Tdap vaccine).⁵⁰ However, on chart review, only half the patients could be confirmed as having a clinical presentation consistent with chorioamnionitis.⁵⁰ This finding supports the interpretation that, in the United States, perhaps because of litigation concerns, many fevers during the third trimester are labeled as chorioamnionitis. Notably, in this study, there was no increase in the risk of preterm birth, which was the main clinical outcome of concern associated with chorioamnionitis.⁵⁰

In another study in the United States, there was no increase in risk associated with concomitant administration of influenza and Tdap vaccines during pregnancy.⁵¹ Similarly, there was no increase in acute events (local reactions, fever, or allergy) or in adverse birth outcomes (preterm delivery, small size for gestational age, or low birth weight) associated with the time since previous receipt of tetanus-containing vaccine.⁵²

Maternal pertussis immunization results in increased concentrations of pertussis antibodies in infants,⁵³ and there is a theoretical concern that these vaccine-induced maternal antibodies might reduce the immunogenicity of infant diphtheria-tetanus-pertussis (DTP) vaccine. Studies evaluating the attenuation of infant DTP responses by infection-derived maternal antibodies have had heterogeneous findings. Overall, however, there was greater attenuation of immunogenicity in infants who received DTP vaccine containing whole-cell pertussis (DTwP) than in those who received DTP vaccine containing acellular pertussis (DTaP).⁵⁴

There are emerging data on the effect of

vaccine-induced maternal pertussis antibodies on infant DTaP responses, whereas apparently no studies have assessed such responses in infants receiving DTwP, the version of pertussis vaccine used in most developing countries. Small trials in the United States¹⁴ and Canada⁵⁵ showed lower antibody responses to DTaP among infants whose mothers received Tdap during pregnancy than among the infants of unvaccinated women. In a small trial in Vietnam (where infants also received DTaP), antibodies against pertactin (an immunogenic virulence factor of *Bordetella pertussis*) but not against pertussis toxin and filamentous hemagglutinin, two other pertussis antigens, were lower in the infants of mothers who received Tdap during pregnancy.^{55,56}

The clinical relevance of studies showing attenuation of vaccine responses in infants is uncertain, since there is no broadly accepted immunologic correlate of protection for pertussis. Nevertheless, these findings warrant monitoring of age-specific pertussis trends in populations with maternal pertussis immunization in order to detect any shifting of the disease burden from infants who are younger than 6 months of age to infants who are 6 months of age or older, as well as to children and adolescents.

MATERNAL VACCINES IN DEVELOPMENT

In recent years, there has been an increase in efforts to develop vaccines for pregnant women. Vaccines against respiratory syncytial virus (RSV) and group B streptococcus have seen the most progress and are discussed here.

RESPIRATORY SYNCYTIAL VIRUS VACCINE

RSV is the leading cause of viral acute lower respiratory tract illness, and the highest morbidity is among preterm infants.^{57,58} In 2005, RSV-related acute lower respiratory tract illness was associated with an estimated 66,000 to 199,000 deaths among children younger than 5 years of age globally.⁵⁷ Most of these deaths occurred among infants, although in developing countries, deaths also occurred in the second year of life. In another study, the estimated number of RSV-associated deaths was higher, and 2 to 3% of all neonatal deaths were attributed to RSV.⁵⁸ In a multisite, U.S.-based surveillance study conducted between November and April (the putative

respiratory infection season), 20% of hospitalizations, 18% of emergency department visits, and 15% of office visits for acute respiratory infections in children younger than 5 years of age were associated with RSV.⁵⁹

The high burden of RSV infection, particularly among young infants, has prompted efforts to develop an RSV vaccine for use in pregnant women. There are several RSV vaccines in preclinical and clinical stages of development. Two surface glycoproteins, RSV F and G proteins, are thought to induce neutralizing antibodies.⁵⁹ An F protein nanoparticle vaccine is being investigated in phase 3 clinical trials involving pregnant women.⁶⁰ Another F protein subunit vaccine is being evaluated in phase 2 trials. Vaccines in early and preclinical development include live attenuated, whole inactivated, particle-based, subunit, nucleic acid, and gene-based vector vaccines.⁶⁰ Given that preterm infants are a high-risk group for adverse outcomes of RSV infection, recommendations concerning the gestational age for RSV vaccination will have to account for adequate antibody transfer for preterm infants.

Early RSV vaccine candidates were associated with adverse events. In the late 1960s, a formalin-inactivated vaccine against RSV was evaluated in multiple studies.^{61,62} In these studies, children who were seronegative before vaccination had an increase in the rates and severity of RSV-associated lower respiratory tract infection,^{61,63} subsequently termed “enhanced RSV disease.” There have been several attempts to characterize and understand enhanced RSV disease. We now know that it is associated with immunization with antigens that are not processed in the cytoplasm, resulting in a lack of protective antibodies and CD4+ helper T-cell priming in the absence of CD8+ T cells.⁶³ This aberrant vaccine-associated immunologic response results in a pathogenic Th2 memory response. As a result, the lungs of affected children are characterized by an excess of eosinophils, neutrophilia, mononuclear-cell infiltration, and immune complex deposition after wild-type RSV infection.⁶³

For several decades, enhanced RSV disease-related safety concerns slowed RSV vaccine development. However, given that the primary biologic mechanism underlying protection of infants through maternal RSV immunization involves transferred maternal antibodies, maternal immunization can bypass immunologic events that

lead to enhanced RSV disease in infants. Moreover, because of the high lifetime exposure to RSV and the fact that enhanced RSV disease is restricted to seronegative persons, the risk of enhanced RSV disease is minimal for vaccinated pregnant women. This notion is supported by the absence of enhanced RSV disease among recipients of RSV monoclonal antibodies and by the results of early-phase clinical trials of maternal RSV vaccination.⁶⁴⁻⁶⁶

GROUP B STREPTOCOCCAL VACCINE

Group B streptococcus is associated with adverse fetal and infant outcomes. Early-onset group B streptococcal infection occurs in neonates who are younger than 7 days of age and is characterized by sepsis without a focus, pneumonia, meningitis, or a combination of these findings.^{67,68} Late-onset group B streptococcal infection occurs in infants who are 7 to 89 days of age and, as compared with early-onset infection, is associated with higher rates of meningitis.⁶⁸ Moreover, invasive group B streptococcal infection in pregnant women is associated with stillbirth.⁶⁷ There is also some evidence of an association between maternal infection and preterm birth.⁶⁹

Invasive group B streptococcal disease in infants is a consequence of transmission of group B streptococcus from colonized mothers during birth. In a multicenter study conducted in the United States in the 1980s, approximately one in five pregnant women had evidence of rectal or vaginal colonization with group B streptococcus at 23 to 26 weeks of gestation.⁷⁰ In the late 1990s, universal maternal screening for group B streptococcus and intrapartum antibiotic prophylaxis were initiated to prevent group B streptococcal disease. These recommendations resulted in reductions in early-onset group B streptococcal disease.⁶⁷ However, there has been no reduction in late-onset disease, and the rates of early-onset disease plateaued more than a decade ago. Moreover, there has been no change in the rates of maternal invasive group B streptococcal disease. A maternal group B streptococcal vaccine could help reduce the burden of group B streptococcal disease, particularly late-onset disease, in infants.

In recent decades, there have been multiple attempts at developing maternal group B streptococcal vaccines. The first-generation vaccines evaluated in clinical trials contained polysaccha-

ride antigens and had heterogeneous immunogenicity. More recently, monovalent and trivalent conjugate vaccine candidates have been evaluated in clinical trials.⁷¹⁻⁷³ The trivalent conjugate vaccine, which has undergone phase 1 and 2 trials, contains capsular serotypes Ia, Ib, and III.^{71,72,74,75} The vaccine was immunogenic and safe in these early-phase trials. Serotypes Ia, Ib, and III cover the majority of cases of group B streptococcal disease in infants in the Americas and Europe.⁷⁶ However, the list of serotypes contributing to infant disease globally includes types II and V.⁷⁶ Hence, a maternal group B streptococcal vaccine targeting the global, rather than regional, disease burden will require inclusion of these serotypes.

FUTURE DIRECTIONS

Maternal vaccines have the potential to provide clinically significant protection for mothers and infants. However, realizing the full potential of

maternal vaccines will require rigorous evaluation of these vaccines in preventing adverse birth outcomes, as well as infant hospitalization and death. Moreover, the immunization delivery system in the United States and globally has traditionally focused on childhood vaccines. Incorporating maternal vaccines into antenatal care has been a challenge in many locations. For example, maternal vaccination in the United States is estimated to be approximately 50% for influenza nationally and 10% for Tdap in 16 states that have data on maternal Tdap vaccination.^{77,78} Evidence-based interventions are needed at the practice, provider, and patient levels to ensure high maternal vaccination.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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