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# *Vaccines in Pregnant Women and Research Initiatives*

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**Abstract:** Successful maternal immunization requires consideration of maternal and infant disease burden, biological factors affecting immune response and placental transport of antibodies, optimal timing of immunization, safety and acceptability. Tetanus, inactivated influenza and acellular pertussis vaccines are recommended during pregnancy; others are recommended when maternal risk of infection is high. The development of new conjugate vaccines for use in adults may reduce global maternal and infant disease burden. Maternal immunization against group B streptococcus is projected to be superior to current preventative strategies in decreasing disease. Further evaluation of maternal immunization strategies to prevent maternal and infant infections is needed.

**Key words:** maternal immunization, vaccines, pregnant women, immunogenic, placental transport, infant disease

Pregnancy and early infancy are times of relative immunosuppression when mothers and infants are vulnerable to an increased infectious disease burden, including those that are vaccine preventable. For example, pregnant women have increased morbidity and mortality from influenza compared with their nonpregnant counterparts. Similarly, infants <6 months of age are over represented in rates of hospitalization, morbidity, and mortality attributable to influenza and pertussis.[1] Other pathogens such as group B streptococcus (GBS) cause a wide spectrum of illness in pregnant women ranging from asymptomatic bacteruria to chorioamnionitis, preterm delivery or intrauterine death, and may result in serious illness, long-term morbidity and death in neonates and young infants.[2] Protection of infants through neonatal immunization is limited by the inability of the neonatal immune system to generate protective antibody responses and the fact that disease may precede that response. The development of interventions to prevent such consequences for pregnant women and their infants is urgently needed. Immunization of pregnant women is one promising strategy that merits consideration.

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## *General Issues for Maternal Immunization*

### BIOLOGICAL CONSIDERATIONS

The induction of protective antibodies in a pregnant woman through immunization is desirable, because of the prospect of protecting 2 persons with a single intervention.[1,3] Preventing infection in pregnant women would eliminate personal and financial costs of treating the disease and any complications, both for the mother and potentially for the fetus at risk of intrauterine infection. However, maternal immunization has potential benefits for the infant beyond the prevention of intrauterine infection. Immunization during pregnancy induces maternal antibodies that can then be passively (and in some cases actively) transported across the placenta to the infant, thus mimicking the compensation for the biological immaturity of the infant immune system that occurs in nature. Such passively acquired maternal antibodies may protect the infant against infection until such time as protection is acquired through the primary immunization series given in infancy (eg, pertussis), until vaccines are available and effective for that age group (eg, influenza recommended for age 6 months and older), or until the period of infant risk is ended (eg, GBS).

Successful protection of mothers and infants through maternal immunization depends on a number of biological factors (Table 1).[1,4] Placental transport of maternal pathogen-specific immunoglobulin G (IgG) starts at week 17 of gestation; however, the amount transported is minimal until approximately 34 weeks of gestation. Therefore, the optimal timing of maternal immunization to protect infants is week 28 to 32 of gestation. This allows time for a robust maternal antibody response, ensuring that high levels of maternal IgG are present when placental transport is most efficient. High levels of maternal pathogen-specific IgG at birth should then result in longer duration of infant protection. This timing needs to be balanced carefully against infectious risks to the mother. For infections like influenza, where the risk of maternal morbidity and mortality is substantial, pregnant women should be immunized as soon as influenza vaccine becomes available, regardless of their gestation.[5–7] Similar principles apply during disease outbreaks. In nonoutbreak situations, where the risk of infant morbidity and mortality greatly

*TABLE 1. Factors to Be Considered Before Implementing Maternal Immunization Program*

| Factor | Consideration |
|---|---|
| Safety | Inactivated vaccines are safe in pregnancy |
| | Live vaccines should be avoided 28 d before and during pregnancy |
| Immunogenicity | Does vaccine induce robust and durable immune response? |
| Timing of immunization | Maternal *and* infant disease burden high: immunize earlier |
| | Infant disease burden higher than maternal: immunize in early third trimester |
| Biological considerations | Placental transport minimal until 34 wk of gestation |
| | Amount of maternal antibody available for transport to infant |
| | Coexisting infection (eg, HIV and malaria ↓ placental transport) |
| | Antibody response*—placental transport of subclass IgG1 > IgG2 |
| | High maternal antibody levels likely to ↓ infant response to vaccines? |
| Implementation | Education for providers and public |
| | Acceptability to public |
| | Logistics and financing |

*IgG1 response to protein antigens; IgG2 response to polysaccharide antigens; conjugation of a polysaccharide to a carrier protein (eg, conjugate vaccines) will induce IgG1 response.

HIV indicates human immunodeficiency virus; Ig, immunoglobulin.

exceeds that of the pregnant woman or where antibody levels are known to wane quickly after immunization (eg, pertussis), postponing immunization of the mother to the third or late second trimester is desirable.[8]

Placental transport of maternal pathogen-specific IgG is affected by factors in addition to gestation and the amount of specific IgG available. Coexistent infections that affect placental integrity such as human immunodeficiency virus or malaria (impairs Fc receptor function) have been shown to reduce placental transport and result in lower infant levels of antibodies against *Haemophilus influenzae* type b (Hib) or measles.[1,4] Conversely, ascending infection from the birth canal enhances antibody transport. Maternal IgG subclass response to vaccine antigens is also important. Antibodies of the IgG1 subclass, induced in response to protein antigens [eg, tetanus toxoid (TT)], are actively and passively transported, resulting in enhanced infant antibody levels compared with antibodies induced by polysaccharide antigens (eg, pneumococcal or meningococcal polysaccharide vaccines), which are skewed toward IgG2 subclass.[1,4] Advances in vaccine development whereby polysaccharide antigens have been chemically conjugated to carrier proteins (eg, pneumococcal, meningococcal, and Hib conjugate vaccines) theoretically should lead to an improved maternal antibody response and a subclass response that enhances placental transport.

The risk-benefit assessment of maternal immunization also needs to account for the phenomenon of maternal antibody interference, the observation that infants with higher levels of maternally derived antibodies for a given infectious agent at the time of initiation of their own immunization series may have lower responses to vaccines against that infection compared with infants with lower maternally derived antibody levels.[9] Maternal interference is explained by the fact that maternal antibodies appear to bind to specific B-cell vaccine epitopes, thus preventing access of infant B cells to the same epitopes and their differentiation into antibody-secreting cells. This has been observed for measles and oral poliomyelitis vaccines, but also has been seen with nonreplicating vaccines such as hepatitis A. Maternal interference may be overcome by delaying vaccine administration, using higher concentrations of vaccine antigen or awaiting decline of maternally derived antibodies.[9]

## SAFETY AND MEDICOLEGAL CONSIDERATIONS

Concerns that maternal immunization poses a risk to the developing fetus are mainly theoretical (Table 1).[1,3,7] Unless the risk of infection for the mother is substantial, most practitioners prefer to postpone immunization until the second trimester or later, thus avoiding concerns related to pregnancy loss and fetal development. However, there is no evidence to suggest harm to mother or fetus from inactivated vaccines in early pregnancy. Live viral vaccines [eg, measles, mumps, rubella (MMR); varicella; intranasal live-attenuated influenza] are generally contraindicated 28 days before onset of and during pregnancy because of the theoretical risk that vaccine virus could be transmitted to the fetus. However, registries of pregnant women who inadvertently received live viral vaccines do not demonstrate either fetal infection or malformation, and although counseling of the pregnant woman about the theoretical risks of infection is necessary, this is not ordinarily an indication to terminate the pregnancy.[7]

Before embarking on a maternal immunization program, it is important to realize that the public perception of safety is equally, if not more, important to successful vaccine uptake. When MMR vaccine was falsely reported to be associated with the development of autism in infants,

the perception that MMR vaccine was unsafe led to a drop in vaccination rates and outbreaks of infection.[10] Despite subsequent large-scale population-based studies proving MMR was safe, this misperception still contributes to vaccine hesitancy among parents. It is easy to see to see how similar misperceptions may arise for maternal immunization because pregnancy complications are common. For example, 75% of conceptions are lost before term, most in the first trimester, and the World Health Organization (WHO) estimates that 15% of clinically recognizable pregnancies result in spontaneous abortion.[3,11] Any pregnancy complication is emotionally charged and the chance that a complication may be mistakenly associated with administration of a vaccine is therefore high. This is an added challenge in educating the public and providers about the safety and potential benefits of maternal immunization.

Fear of litigation on the part of vaccine manufacturers and public health officials is a major barrier limiting development of vaccines for use in pregnant women. This fear also limits immunization during pregnancy in resource-rich countries.[3] Despite the fact that safety concerns are theoretical, that evidence from pregnancy registries is reassuring and the potential benefits are compelling, contemporary studies of vaccines in pregnant women are lacking. This results in vaccines being given "cautious" labels for use in pregnancy by regulatory agencies responsible for vaccine licensure. The benefits of maternal immunization for mothers and infants should be increasingly appreciated by the scientific and medical community, and as new vaccines are developed, advice of regulatory agencies and legal entities experienced in dealing with vaccine compensation issues should be proactively sought. This would allow development of appropriate clinical trials to yield the evidence required to secure licensure of vaccines for use in pregnant women. Also, compensatory mechanisms similar to those that exist for the childhood immunization program should be developed and should facilitate planning for appropriate education of the public.

## ACCEPTABILITY OF MATERNAL IMMUNIZATION

Even when maternal immunization has proven safety and efficacy for mother and infant, it remains an under-utilized and under-accepted strategy in resource-rich countries. Although influenza immunization was recommended for pregnant women in 1996, immunization rates in pregnancy before the 2009 H1N1 pandemic were < 15% nationally and approximately 40% after intensive implementation programs.[1] Immunization rates improved during the 2009 to 2010 pandemic and remained at approximately 50% during the subsequent season.[12] However, these rates are much lower than those attained in maternal immunization initiatives in the developing world (eg, elimination of maternal and neonatal tetanus), or those attained in childhood or adolescent immunization programs.

The reasons for poor compliance with maternal immunization recommendations are multifactorial. First, although maternal immunization is not new and was studied as a preventative strategy for pertussis and influenza in the middle of the 20th century,[1,13] this platform is a new initiative for populations in resource-rich countries. Second, the target population is predominantly healthy adults who may be unaware of the need for immunizations throughout their lifetime. Third, pregnant women are encouraged, through print media, TV, and increasingly internet blogs and social media, to avoid ingesting or coming into contact with any potentially harmful substances while pregnant. The potential for misinformation through any of these sources is considerable, and may make education on the part of health care providers (HCPs) more challenging.

Fourth, maternal immunization requires advocacy on the part of HCPs for pregnant women, who may be relatively unfamiliar with the severity of vaccine preventable diseases (VPDs) in mothers and young infants and who, traditionally, have not provided immunizations. Finally, there are logistical and financial barriers to overcome. Maternal immunization requires that obstetric HCPs educate themselves and mothers, as well as stock and administer vaccines. This is a challenging, time-consuming, and cumbersome process for those unfamiliar with this paradigm, but it is worthwhile. Data from the Centers for Disease Control and Prevention (CDC) from the 2010 to 2011 season shows that pregnant women whose HCP offered them influenza vaccination were 5-fold more likely to receive it than those whose HCP did not.[12] This suggests that, as has been shown for infant immunization,[10] obstetric HCPs attitudes and willingness to provide education about the value of vaccines is the greatest influence on a pregnant woman's ultimate decision to receive a vaccine.

## *Immunizations Currently Recommended for Pregnant Women*

### TETANUS

TT during pregnancy is the most widely accepted vaccine worldwide. Historically, maternal immunization with TT vaccines developed in response to the unacceptably high rate of neonatal deaths (6.7 per 1000 births) attributable to tetanus globally. In 1989, the World Health Assembly called for elimination of neonatal tetanus (defined as $<1$ case per 1000 live births) by 1995. Subsequently, this was revised due to slow implementation of preventative strategies and adding the goal of maternal tetanus elimination. Key components in preventing tetanus are promotion of hygienic obstetrical practices and maternal immunization. Tetanus is an example of a protein-based vaccine that is safe when administered to pregnant women. It stimulates the production of TT-specific IgG that is actively transported across the placenta and is effective in preventing maternal and neonatal infection whether administered before or during pregnancy (Table 2).[1] Maternal and neonatal tetanus is concentrated in resource-limited countries where women of child-bearing age may not have been immunized. The Maternal Neonatal Tetanus (MNT) initiative recognizes that the antenatal clinic is a very useful point of contact for these women, and the WHO recommends 2 doses of TT in the first and 1 in each subsequent pregnancy until 5 doses are given to ensure protection throughout child-bearing years. Countries that eliminated tetanus under this initiative achieved maternal immunization rates in excess of 80%. The MNT initiative resulted in a 92% reduction in annual neonatal deaths from 1988 to 2008; however, as of September 2011, 39 countries had not met the WHO standard for tetanus elimination.[14]

In resource-rich countries, tetanus immunization is recommended at 10-year intervals after completing the primary immunization series in childhood. In the United States, pregnant women not vaccinated within the previous 10 years should receive tetanus given in combination with diphtheria toxoids (Td) and acellular pertussis (Tdap) if indicated. Pregnant women whose immunization status is unknown or incomplete should receive Td at an interval of 0, 4 weeks and 6 to 12 months with a dose of Tdap replacing one of the Td during the third or late second trimester.[8]

### INFLUENZA

In 1996, the CDC recommended that all women in the United States who would be pregnant during the influenza season receive inactivated trivalent influenza vaccine (TIV). This recommendation, driven by

***TABLE 2. Vaccines Recommended* or High Priority for Investigation† During Pregnancy***

| Vaccine | Safe | Immunogenic in Mothers | Placental Transport | Antibodies Persist? | Indication or Stage of Study |
|---|---|---|---|---|---|
| Tetanus-diphtheria toxoid*‡ | Y | Y | >100% | Y | Prevent maternal and neonatal tetanus |
| Influenza, inactivated* | Y | Y | 94%-99% | ≥2 mo | Prevent maternal and infant influenza |
| Meningococcal, polysaccharide*§‖ | Y | Y | 30%-56% | 3-4 mo | Phase 1 studies performed |
| Pneumococcal polysaccharide*§ | Y | Variable by serotype | 24%-89% | Y | Phase 1 studies performed |
| Acellular pertussis (Tdap) * | Y | Y | >100% | ND | Prevent infant mortality from pertussis<br>Phase 1 studies ongoing |
| Group B Streptococcus, conjugate†¶ | Y | Y | 77% | ≥2 mo | Phase 1 studies performed<br>Phase 1 and 2 studies ongoing |
| *Haemophilus influenzae* type b, conjugate† | Y | Y | 35%-61.5% | 4-6 mo | Phase 1 studies performed |
| *Haemophilus influenzae* type b, polysaccharide† | Y | Y | 44% | 4-6 mo | Phase 1 studies performed |
| Meningococcal, conjugate† | ND | ND | ND | ND | ND |
| Pneumococcal conjugate† | ND | ND | ND | ND | ND |
| Respiratory syncytial virus† | Y | Moderately | >100% | 6 mo | Phase 1 studies performed |

Reproduced from Healy and Baker.[1]
‡Not previously immunized or booster is required.
§Underlying medical conditions.
‖Endemic or epidemic exposure.
¶Results shown are for GBS type III conjugate vaccine, phase 1 and 2 trials ongoing for new candidate conjugate vaccines.
ND indicates not determined; Y, yes.

excessive mortality and morbidity in pregnant women during annual influenza epidemics and previous pandemics (in excess of 50% during the 1918 pandemic), was originally recommended for second and third trimester administration; this was amended to allow for TIV at any stage during pregnancy.[1,7] During the 2009 to 2010 H1N1 pandemic, pregnant women were again over represented in influenza-related morbidity and mortality, and accounted for 5% of all deaths while only representing 1% of the population. Infants less than 6 months of age, for whom no vaccine is licensed, generally have the highest influenza hospitalization rates and account for the majority of infant deaths. These infants are dependent solely on maternally acquired influenza-specific IgG and on targeted immunization of all their contacts (cocooning) for protection.

Influenza vaccination in pregnancy was established as safe during the 1950s and 1960s when 2291 pregnant women were immunized; no vaccine-related adverse events were seen in their infants over a period of 7 years follow-up.[1] Subsequent studies have confirmed that TIV in pregnancy is safe and immunogenic in the mother. Further, recent studies performed in Bangladesh and the United States demonstrated that immunization of pregnant women effectively reduced laboratory-confirmed influenza, influenza-like illness, and influenza-related hospitalizations in their infants (Table 2).[1,15,16] There are data suggesting that receiving TIV in pregnancy may reduce the risk of

countries and even if these issues were overcome, the age of onset of disease often precedes the first dose of vaccine (given at 6 to 8 wk of age).

Single-dose maternal immunization is an alternative strategy to protect young infants. When 23-valent pneumococcal polysaccharide vaccines were administered to pregnant women during the third trimester, they were safe and immunogenic. Variable immune responses occurred by pneumococcal serotype and placental transport was variable (24% to 89%).[1] The prospect that protection could be enhanced by immunizing pregnant women with pneumococcal conjugate vaccine is demonstrated by studies where placental transport of IgG1 antibodies to some pneumococcal serotypes was higher than for IgG2 antibodies and that low IgG1 (not IgG2) predicts early infant otitis media. In addition, there is some evidence that immunized mothers have higher levels of specific IgA in their breast milk for 4 to 6 months after delivery and adherence of serotype 14 pneumococci to epithelium is reduced in vitro when colostrum from immunized mothers is present. Further, animal studies have suggested enhanced immune responses in infant mice when high maternal antibody is present rather than interference. One of the disadvantages of pneumococcal vaccines, however, is that protection is limited by the number of included serotypes and studies to date show inconsistent results on their ability to reduce nasopharyngeal carriage, a presumed precursor to developing invasive disease.[1] Future research in this area also is focused on developing protein-based vaccines that may be effective in giving serotype independent protection against pneumococcal carriage and disease.

## MENINGOCOCCUS

Invasive meningococcal disease (IMD), caused by *Neisseria meningitidis*, is predominantly caused by serogroups A, B, C, Y, or W135, although sporadic cases of serogroup X disease occur in Africa. In resource-rich countries, mortality and morbidity rates reach 5% to 10% and 20%, respectively, and are considerably higher in resource-limited countries.[19] Both meningococcal polysaccharide and conjugate vaccines are available to protect against serogroups A, C, Y, and W135. Prevention of serogroup B disease has to date been hampered by poor immunogenicity of the capsule and need to cover multiple subtypes; reverse and structural vaccinology techniques are ongoing to develop a safe and broadly protective vaccine. However, most maternal and neonatal disease is potentially vaccine preventable. In sub-Saharan Africa, an area known as the "meningitis belt," annual outbreaks of IMD occur with high mortality and morbidity.[19] In the United States, infection rates in the first month of life are similar to those in older infants. Serogroup B disease predominates in young infants, but other serogroups may cause up to 50% of IMD cases. Peaks attack and mortality rates are before 3 to 4 months of age in the United States, a time that coincides with the likely waning of maternal immunity and before the time at which immunity from infant vaccines (2 are currently pending licensure) may be expected.

Maternal immunization with meningococcal polysaccharide vaccines was studied in Africa. These were found to be safe and immunogenic in mothers and induced maternal antibody levels that were 4- to 7-fold higher in immunized mothers than controls against groups A and C, respectively. Placental transport varied from 30 % to 56% and maternal antibody persisted until age 3 to 4 months. Further, immunization during pregnancy induced IgA against serogroup A in breast milk that persisted until infant age of 6 months.[1]

Meningococcal serogroup C conjugate vaccines administered in the infant,

childhood, and adolescent schedules have been extremely effective in reducing serogroup C disease in Europe and Canada where this serogroup predominated.[19] In the United States, where serogroup prevalence is more diverse, 2 meningococcal quadrivalent A, C, Y, W135 conjugate vaccines are licensed (1 from age 9 mo to 64 y, 1 from age 2 through 64 y), and are recommended for routine use in adolescence and for high-risk individuals in other age groups. Two conjugate vaccines, a quadrivalent A, C, Y, W135 and a bivalent A, C, Hib are pending licensure for use in infants. No meningococcal conjugate vaccines have been studied in pregnancy, although no safety concerns were reported when pregnant women received these inadvertently. These conjugate vaccines would likely offer greater potential benefit than their polysaccharide counterparts which are recommended for use in pregnant women in high-risk situations. Conjugate vaccines would likely generate T-cell–dependent maternal responses, immune memory, and longer term protection. Placental transport would likely be improved through induction of subclass IgG1 maternal antibodies resulting in onger lived immunity in young infants.[1] Data from nonpregnant populations also suggest that they may prevent maternal nasopharyngeal carriage thus limiting intrafamilial spread.[19] Maternal immunization with meningococcal conjugate vaccines is a strategy that could potentially save countless lives in resource-limited countries. In areas such as the United States, where disease incidence is currently low, it is a strategy that could significantly reduce infant mortality and morbidity if introduction into the infant schedule is not a priority or not cost effective.

## RESPIRATORY SYNCYTIAL VIRUS (RSV)

RSV causes epidemic viral respiratory disease in infants with disease rates peaking in the second month of life. RSV accounts for substantial morbidity and mortality in early infancy, and candidate vaccines have not been immunogenic nor well tolerated in infants. Studies suggest that IgG1 antibody to the RSV fusion protein correlates with protection in infants and that high levels of antibody will protect against severe disease. A purified fusion protein subunit vaccine against RSV was studied in pregnant women.[20] This vaccine was safe and modestly immunogenic but demonstrated excellent placental transport of antibodies that persisted until the infant was 6 months of age. RSV represents a maternal immunization target should more immunogenic candidate vaccines become available.

## GBS

A safe and immunogenic GBS vaccine is the ideal candidate vaccine for use in pregnancy. Although GBS is increasingly recognized as a pathogen in nonpregnant adults, especially the elderly, severe invasive disease occurs in young infants and in pregnant women. Early-onset GBS (EOGBS) in infants occurs before age 7 days and commonly presents as sepsis (80% to 95%), pneumonia (10% to 15%), or meningitis (5-10%). Severity of illness ranges from healthy appearing infants to multiorgan failure and death (mortality of 2% to 20% for term and preterm infants, respectively). Late-onset GBS (LOGBS) occurs in infants aged 7 to 89 days, presents less commonly with overwhelming sepsis and more commonly with meningitis; whereas mortality is lower than that for EOGBS (1% to 6%), up to one third of cases have permanent sequelae (hearing loss, developmental delay, etc.).[2,21] Late-late-onset GBS occurs in infants older than age 89 days (most often in preterm infants whose corrected gestational age is less than age 3 mo). Recurrent GBS is reported in an estimated 0.5% to 3% of infant disease.

Maternal GBS infection can lead to asymptomatic bacteruria, urinary tract

infection, or pyelonephritis during pregnancy, and bacteremia, chorioamnionitis, or postpartum endometritis in the peripartum period. GBS also can result in spontaneous abortion, preterm delivery, or stillbirth. In most countries, approximately 95% of invasive GBS in mothers and infants is caused by 5 GBS capsular polysaccharide types, types III, Ia, V, Ib, and II in decreasing frequency.[2,21]

Lower vaginal or rectal colonization with GBS in women of child-bearing age is common. Carriage rates of 30% overall are reported in pregnant women with higher rates reported in those of African American ethnicity. GBS colonization in pregnant women is a prelude to maternal disease and EOGBS in the infant. GBS screening in late pregnancy and intrapartum antibiotic prophylaxis (IAP) of women found to be positive reduced the rate of EOGBS in the United States from 1.7 per 1000 live births in 1993 to 0.26 to 0.37 per 1000 live births between 2005 and 2009, and invasive disease in pregnant women to 0.12 per 1000 deliveries. Not surprisingly, the rate of LOGBS did not change over the same period (0.25 to 0.6 per 1000 live births) as eradication of carriage subsequent to IAP is short lived. Despite the success of IAP, the eventual emergence of resistant GBS strains is a concern while relying on this preventative strategy.[21]

Early research and development of candidate GBS vaccines started in the 1970s with observations that mothers of GBS-infected infants had very low levels of serum GBS capsular polysaccharide-specific antibodies at delivery. This was followed by observations that "sufficient" quantities of GBS capsular polysaccharide-specific IgG could promote opsonization and phagocytosis of GBS strains in vitro and protect from lethal experimental infection. Disappointingly, studies of the first polysaccharide GBS vaccines had capsular type variable immunogenicity in pregnant and nonpregnant adults. In the single maternal immunization study performed, polysaccharide vaccines were well tolerated and infants of vaccine responders had functionally active GBS antibodies at age 2 to 3 months that, in the presence of infant complement and polymorphonuclear cells, killed type III GBS in vitro.[21]

The advent of conjugate vaccine technology and the success these vaccines had in controlling infant Hib and pneumococcal disease would have been expected to accelerate the development of a GBS vaccine. This did not happen as rapidly as hoped, possibly because of concerns about the acceptability and implementation of the maternal immunization platform. Conjugate vaccines were developed by researchers at Harvard Medical School and Baylor College of Medicine for types Ia, Ib, II, III, V, and a bivalent II/III. Phase 1 and 2 studies in nonpregnant adults demonstrated that these conjugate vaccines were well tolerated, immunogenic, and defined optimal doses of GBS capsular polysaccharide to be used in future multivalent conjugate GBS vaccines. Further, more than 80% of adult vaccine recipients developed 4-fold higher antibody levels that declined by 50% in the year after immunization, but persisted at higher than baseline levels 2 to 5 years later. In the single maternal immunization study of a type III conjugate vaccine, maternal antibody was 55-fold higher than preimmunization levels, placental transport was 77% and maternal antibodies in infants (that were predominantly of the IgG1 subclass) promoted killing of type III GBS in vitro at age 2 months.[21]

There are reasons to be optimistic that new GBS vaccines will be available and licensed within the next decade, after the almost 40 years of research and development outlined here. The European Union's 7th Framework Program for Research and Technological Development funded the DEVANI (DEsign a Vaccine Against Neonatal Infections) project in

2008. DEVANI's mission is to develop immunization strategies that would result in durable immunity against GBS in pregnant women and protect offspring through the period of risk for invasive GBS.[22] New candidate trivalent polysaccharide-protein conjugate vaccines are being tested in phase I and II studies in both pregnant and nonpregnant adults. Research into alternative strategies, such as using different GBS proteins as vaccine candidates and reverse vaccinology techniques, are ongoing.[21]

An effective GBS vaccine will have important implications not only for obstetricians and pediatricians, but also for public health officials. Mathematical modeling of IAP and a number of GBS vaccination strategies (adolescent, maternal, or postpartum), assuming an effective multivalent vaccine, suggest both adolescent and maternal immunization are more effective than IAP.[23] Maternal immunization was most effective and was estimated to potentially prevent 4% of preterm births, 61% to 67% of EOGBS and 70% to 72% of LOGBS. Maternal immunization will undoubtedly have the most profound and immediate effect on GBS disease rates. Alternative strategies also need to be considered for longer term disease control, such as administering a dose of vaccine in adolescence with perhaps booster doses preconception or during pregnancy and studies to determine the optimal timing and frequency of such booster doses throughout the child-bearing years will be needed.[21]

## The Future of Maternal Immunization

Maternal immunization is a promising platform with the potential to produce health benefits for both mother and infants. Further, it may be argued that this immunization platform, although a new one, is the most natural, mimicking as it does mother's gift of natural immunity to her offspring. This maternally derived immunity may then protect through the early months of life when infants are especially are vulnerable to infections that either target them selectively or are more particularly severe in infancy. Major barriers limiting this platform, at least in resource-rich countries, are concerns regarding liability issues and the acceptability of this strategy. Developing this platform will also have financial implications globally. Further, there is a need to educate both providers and patients. These concerns have delayed research into developing this platform. There are indications that this will change. The success of the MNT initiative in eliminating this disease, albeit slower than had been projected, is a powerful reminder of the potential health benefits. Likewise, immunizing pregnant women against influenza was one of the most important initiatives targeted by most countries during the 2009 H1N1 pandemic. The recent recommendation of the CDC to immunize pregnant women against pertussis, a move that is solely intended to benefit the infant, is yet another example of this change in attitude. Finally, advances in GBS vaccine development where studies in pregnant women are underway optimistically predict that this platform is emerging and will eventually be a powerful tool to reduce maternal and infant morbidity and mortality from infection.

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