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The Impact of IgG Transplacental Transfer on Early Life Immunity

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ABSTRACT

Pediatric vaccines have significantly reduced infectious disease–related infant mortality, but as protective immunity often requires several infant vaccine doses, maternally acquired Abs are critical to protect infants during the first months of life. Consequently, immunization of pregnant women is an important strategy not only to protect mothers from infection, but also to provide immunity to young infants. Nevertheless, maternal immunization can also negatively impact early life immunity. In fact, maternal Abs can interfere with the development of infant immune responses, although it is unclear whether such interference is clinically significant. Moreover, the transplacental transfer of maternal Ig therapeutics can be harmful to the fetus. Thus, the risk–benefit of maternal immunization for both the mother and the fetus should be carefully weighed. In addition, it is critical to fully understand the mechanisms by which IgG is transferred across the placenta to develop optimal maternal and infant immunization strategies.


INTRODUCTION

The World Health Organization estimates that 5.9 million children <5 y of age died in 2015, with >40% of these deaths due to infectious diseases (1). Children are particularly vulnerable during the neonatal period as 45% of deaths of children <5 y old occur during the first month of life. Maternal Abs transferred to the fetus in utero across the placenta and through breastfeeding are critical to protect infants from infections during the first months of life. Vaccination during pregnancy to boost maternal Ab levels and enhance infant passive immunization has been effective to fight against some neonatal infections such as tetanus (2, 3). Nevertheless, the incidence of other neonatal pathogens such as pertussis has increased over the last three decades (4). Importantly, even when infants passively acquire protective levels of pertussis-specific IgG, these Abs rapidly wane during the first 2 mo of life, leaving the infant vulnerable to infection (5, 6). In contrast, licensed maternal vaccines are not yet available against some life-threatening neonatal pathogens such as group B streptococcus (GBS) or respiratory syncytial virus (RSV). Novel approaches to extend the period during which infants are protected by maternal Abs, as well as novel maternal vaccines, would be critical to reduce infectious disease–related neonatal and infant mortality.

The Fc neonatal receptor (FcRn) has been demonstrated to play a critical role in mediating IgG transplacental transfer (7, 8), but recent studies demonstrating distinct transfer efficiencies of...
different epitope-specific IgG suggest that other mechanisms could also contribute to the regulation of IgG transfer. This review summarizes current knowledge on the mechanism of IgG transplacental transfer and on factors associated with impaired IgG transfer. In addition, the potential benefits and harms of IgG transplacental transfer on the fetus and the timing of maternal immunization for optimal transplacental transfer are discussed.

MECHANISMS OF IgG TRANSPLACENTAL TRANSFER

To be transferred from the maternal to the fetal circulation, IgG must cross several anatomical barriers. In fact, the fetal and maternal circulatory systems are separated by placental treelike floating villous structures made up of syncytiotrophoblasts in the outermost cell layer, with a cytotrophoblast cell layer directly beneath (9). The villous trees contain fetal blood vessels, which feed into the umbilical cord and ultimately into the fetal circulatory system (9). To reach the fetal circulation, maternal IgG must cross the syncytiotrophoblast and cytotrophoblast cell barriers and then be transferred across the villous stroma to ultimately reach the lumen of fetal endothelial vessels.

Role of FcRn in IgG transplacental transfer

FcRn is a MHC class I-related molecule (10) that plays a central role in the regulation of IgG homeostasis and in IgG transport across polarized epithelial barriers (11, 12). It is expressed by a variety of cells including epithelial cells, endothelial cells, and myeloid-derived APCs. Expression of FcRn on APCs appears to be crucial for efficient IgG-mediated phagocytosis (13), whereas expression on endothelial cells is important to prolong IgG half-life by recycling internalized IgG back to the surface (14). Early studies have demonstrated that the FcRn expressed on syncytiotrophoblast cells is a key contributor to IgG transplacental transfer (15, 16). FcRn is mostly present in the cytosol, and it binds the Fc portion of IgG at acidic pH (17, 18). It is thought that maternal IgG in the intervillous space undergoes fluid-phase endocytosis into syncytiotrophoblast cells into endosomes that undergo slight acidification (12, 19–21). FcRn then binds to maternal IgG in these mildly acidic endosomes and is carried to the basal plasma membrane, where IgG is released from FcRn upon exposure to normal pH in inside the villous tree (12). Yet, several steps in the IgG transport across the placenta remain incompletely understood. For example, the mechanism by which maternal IgG enters syncytiotrophoblast cells from the intervillous space is not completely elucidated (12, 16), nor is the mechanism by which maternal IgG is transported through the villous stroma. Importantly, aside from FcRn, several other Fcy receptors are expressed in the placenta (Table I), but their physiologic relevance is not understood. Notably, Hofbauer cells contained in the villous stroma express FcγRI, FcγRII, and FcγRIII (22), and fetal endothelial cells express the low-affinity monomeric IgG receptor FcγRIIb (15, 23, 24). Future studies should therefore focus on elucidating the mechanism of IgG transplacental transfer across the distinct placental anatomical barriers and explore the role of placental Fcy receptors in modulating IgG transfer.

Timing of IgG transfer during gestation

The transplacental transfer of maternal IgG to the fetus begins during the first trimester of pregnancy. In fact, maternal IgG can be detected in cord blood as early as 8–10 wk of gestation (7). However, only small amounts of maternal IgG are transferred in the first trimester, with an estimated transplacental transfer of ~10% of maternal IgG concentrations by 17–22 wk of gestation (25). The concentration of maternal IgG in infant cord blood reaches ~50% of the maternal IgG levels by 30 wk of gestation (25) and by 37–40 wk of gestation, infant cord blood concentrations of maternal IgG often exceed that of maternal serum by the delivery time point in full-term, healthy pregnancies (25–28). Thus, although maternal IgG is transferred across the placenta throughout pregnancy, the majority of the transfer occurs in the last trimester of gestation, possibly because of an increase in the surface area of IgG uptake from maternal blood with older gestational age. Yet, certain pathologic conditions of the placenta and maternal immunity can impair the efficiency of placental IgG transfer, including maternal HIV-1 and malaria infections. The timing and efficiency of the IgG transplacental transfer have important implications for the development of maternal immunization strategies to protect infants.

Passively acquired maternal Abs with different Ag specificity have been reported to have distinct half-lives in infants. For example, although in normal pregnancy pertussis-specific IgG levels in cord blood achieve >100% of maternal levels, maternal pertussis-specific IgG has a half-life of 6 wk in infants and wanes to undetectable levels as early as 4 mo of life (29). In contrast, maternal passively acquired measles-specific IgG remains near or above protective levels in 6-mo-old infants and are still detectable by 1 y of life (30, 31). This suggests that maternally acquired measles-specific IgG compared with pertussis-specific IgG may have slower decay rates in infants. It remains unclear why different maternally acquired IgG responses have distinct decay rates in infants. However, the distinct half-lives of pertussis and

<table>
<thead>
<tr>
<th>Placental Fc Receptor</th>
<th>FcγRI (CD64)</th>
<th>FcγRII (CD32)</th>
<th>FcγRIII (CD16)</th>
<th>FcRn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trophoblasts</td>
<td>– (139, 140)</td>
<td>– (139, 140)</td>
<td>+ (139–144)</td>
<td>+ (15, 16, 18, 145)</td>
</tr>
<tr>
<td>Stromal cells</td>
<td>+ (140, 143)</td>
<td>+ (140)</td>
<td>+ (140)</td>
<td>NR</td>
</tr>
<tr>
<td>Hofbauer cells</td>
<td>+ (139–141, 143)</td>
<td>+ (139–141, 143, 146)</td>
<td>+ (139, 142, 143)</td>
<td>NR</td>
</tr>
<tr>
<td>Fetal endothelial cells</td>
<td>– (139, 140)</td>
<td>+ (24, 139–141, 143, 147)</td>
<td>+ (140)/ – (139)</td>
<td>– (15, 16)</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate reference numbers. +, detected; –, not detected; NR, not reported.

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measles-specific IgG in infants could, in part, be due to: 1) distinct Fc region characteristics such as IgG subclass or Fc region glycans, or 2) distinct interactions with the IgG recycling receptor in humans: FcRn. A deeper understanding of the mechanism(s) of the distinct kinetics of maternally acquired Ag-specific IgG in infants is critical to guide the development of strategies to increase the durability of maternally passively acquired IgGs and ultimately extend the window of Ab-mediated protection in the first year of life.

IgG characteristics that modulate IgG transplacental transfer
The efficiency of IgG transfer can vary from one Ag specificity to another. For example, in normal pregnancy the transfer efficiency of IgG against pertussis can be up to 200%, whereas for GBS it is only 70% (32, 33). Distinct characteristics of Ag-specific Abs may contribute to explain these differences. Several reports have indicated that IgG subclass is an important determinant of transplacental transfer efficiency. IgG1 is the most efficiently transferred subclass, whereas IgG2 is transferred with the least efficiency (34, 35). Importantly, IgG subclass responses are distinctly modulated against different Ags (36). For example, the IgG response against polysaccharide Ags such bacterial capsule of GBS or *Haemophilus influenzae* type B is primarily IgG2 subclass, whereas the response against tetanus toxoid is predominantly IgG1 (28, 36). In addition to IgG subclass, Ab avidity (37, 38) and Fc region glycosylation profile may influence transplacental transfer (39, 40). The affinity of IgG binding to the canonical FcRn may also contribute to modulate the transplacental transfer efficiency. In fact, the highly transferred IgG1 and IgG4 subclasses have comparably high affinity to FcRn, whereas both IgG3 and IgG2 had lower affinities for FcRn (41). The differential transfer of Abs of distinct subclasses has important implications for the development of mAb therapeutics used during pregnancy.

Factors that impair IgG transplacental transfer
Transplacental transfer of maternal IgG is a highly efficient process in healthy pregnancies. In fact, infant cord blood concentrations of maternal IgG can well exceed maternal IgG serum concentrations by delivery in full-term pregnancies (25–27). However, several factors can impair IgG transplacental transfer, including maternal infections during pregnancy (i.e., HIV and malaria), placental pathologies, and maternal hypergammaglobulinemia.

Placental malaria has been associated with reduced IgG transplacental transfer of malaria and vaccine antigen-specific IgG (42–45). Although the mechanism of this impaired IgG transfer remains unclear, studies have demonstrated that placental malaria leads to placental pathologies through an increased influx of monocytes, macrophages, and cytotoxic T cells into the placental intervillous space (46). Several studies have also indicated that HIV-exposed uninfected infants have lower levels of maternal Abs than their unexposed counterparts (42, 45, 47–50). In fact, maternal HIV infection has been associated with poor transfer of Abs against some pathogens including *Streptococcus* pneumonia, *H. influenzae*, GBS, pertussis, poliomyelitis, and measles (reviewed in Ref. 51). In contrast, reports on the impact of maternal HIV on the transfer of other Ab specificities, such as anti-tetanus toxoid Abs, have been variable between studies and populations (reviewed in Ref. 51). It was recently reported that women who are receiving long-term antiretroviral therapy have improved IgG transplacental transfer compared with women who receive a short course of antiretroviral therapy (52). Importantly, some studies have suggested that maternal HIV infection may also impact the quality of the transferred Abs (53, 54). This observation needs to be confirmed in large cohorts of HIV-infected mothers and HIV-exposed uninfected infants.

Maternal hypergammaglobulinemia, which is characterized by abnormally high levels of serum Ig, has also been associated with poor IgG transfer (44, 55). Notably, HIV- and malaria-induced maternal hypergammaglobulinemia was independently associated with poor transfer of IgG against tetanus toxoid, measles, and RSV (42, 56). Although it remains unclear how high maternal IgG serum levels interfere with IgG transplacental transfer, a potential mechanism could be the saturation of placental shuttle Fc receptors such as FcRn. Understanding the mechanism by which maternal pathologies lead to poor IgG transplacental transfer is crucial to devise optimal maternal immunization strategies to extend the window of infant protection against common neonatal pathogens during the first year of life.

MATERNAL IMMUNIZATION TO PROTECT INFANTS FROM NEONATAL PATHOGENS
Pregnancy is associated with a specific immunologic milieu, as the maternal immune system needs to tolerate the fetus allograft. As a result, some infections are more severe in pregnant women than in their nonpregnant counterparts. For example, influenza-related hospitalization and mortality are higher in pregnant women (57–60). The most effective way to protect pregnant women from the morbidity associated with infections is to vaccinate them against vaccine-preventable diseases (3). Maternal vaccination has the added benefit of protecting infants because Abs are transferred to the fetus across the placenta. Protection of infants from maternal immunity was first observed in the 1800s during a measles outbreak among women who survived the disease were protected (61). More recent studies have demonstrated that similar to disease-induced IgG, vaccine-elicited IgG Abs are efficiently transferred across the placenta (62, 63). Currently, vaccines routinely administered during pregnancy include influenza and tetanus, diphtheria, and acellular pertussis (Tdap). In addition, some vaccines such as those against pneumonia, meningococcus, hepatitis A, and hepatitis B are recommended during pregnancy under specific circumstances (Table II).

Vaccines routinely administered during pregnancy
*Influenza vaccine.* Influenza viruses represent one of the most significant causes of acute upper respiratory tract infections...
TABLE II. Maternal vaccine recommendations in the United States

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Type</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routinely administered vaccines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tdap</td>
<td>Toxoid/inactivated</td>
<td>All pregnant women</td>
</tr>
<tr>
<td>Influenza</td>
<td>Inactivated</td>
<td>All women pregnant during the influenza season</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Live attenuated (LAIV)</td>
<td>Prior to travel, history of injection of illicit drug, professional exposure, chronic liver disease</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Inactivated</td>
<td>Prior to travel, sexual exposure, drug usage</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>Inactivated</td>
<td>Risk–benefit assessment</td>
</tr>
<tr>
<td>MMR</td>
<td>Live attenuated</td>
<td>Contraindicated during pregnancy; postpartum if rubella nonimmune</td>
</tr>
<tr>
<td>Pneumococcal PCV 13</td>
<td>Conjugate</td>
<td>No recommendation</td>
</tr>
<tr>
<td>Pneumococcal PPSV23</td>
<td>Polysaccharide</td>
<td>Inadequate data</td>
</tr>
<tr>
<td>Poliomyelitis (IPV)</td>
<td>Inactivated</td>
<td>Use if needed</td>
</tr>
<tr>
<td>Varicella</td>
<td>Live attenuated</td>
<td>Contraindicated during pregnancy; postpartum if varicella nonimmune</td>
</tr>
<tr>
<td>Zoster</td>
<td>Subunit</td>
<td>Contraindicated during pregnancy</td>
</tr>
<tr>
<td>Anthrax</td>
<td></td>
<td>Vaccination not recommended in pre-event setting; may be used if high risk of exposure in postevent setting</td>
</tr>
<tr>
<td>BCG</td>
<td>Live</td>
<td>Inadequate data for specific recommendation</td>
</tr>
<tr>
<td>Japanese encephalitis virus</td>
<td>Inactivated</td>
<td>Use if needed</td>
</tr>
<tr>
<td>Typhoid</td>
<td>Live and inactivated</td>
<td>Inadequate data; use Vi polysaccharide vaccine if needed</td>
</tr>
<tr>
<td>Rabies</td>
<td>Inactivated</td>
<td>May be used if needed</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Live attenuated</td>
<td>Risk–benefit assessment</td>
</tr>
</tbody>
</table>

BCG, bacillus Calmette–Guerin; LAIV, live attenuated influenza vaccine; MMR, measles mumps and rubella; PCV, pneumococcal conjugate vaccine.
From the guidelines of the 2016 Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (148).

Surprisingly, although the virus causes morbidity in all age groups, influenza-associated complications and hospitalization rates are higher among pregnant women (60, 64, 65), and young infants (66, 67). Maternal immunization is critical to protect young infants because there is currently no licensed influenza vaccine capable of eliciting an immunogenic response in infants younger than 6 mo. Thus, young infants are left unprotected during a period when they are susceptible to development of severe complications. The safety, immunogenicity, and efficacy of a trivalent influenza vaccine were recently evaluated in HIV-infected and uninfected women from South Africa (clinicaltrials.gov numbers NCT013066669 and NCT01306682). The vaccine was found to be immunogenic and partially protective in both populations of pregnant women (68). Moreover, maternal vaccination was associated with protection of infants from PCR-confirmed influenza illness. But the protection was short-lived (first 8 wk of life) and correlated with a decrease in maternally acquired Abs (6). A longer period of infant protection (4 mo) was observed following immunization of pregnant women from Mali during the third trimester of gestation (69). Maternal vaccination was also associated with reduced rates of laboratory-confirmed influenza in a phase 4 randomized trial conducted in Nepal [clinicaltrials.gov number NCT01034254 (70)] and with reduced influenza-related infant hospitalization in the United States (71).

**Tetanus, diphtheria, and pertussis vaccines.** A different setting in which maternal vaccination is critical for infant protection is when several doses of vaccine are required to achieve protective immunity in infants. This is the case for tetanus, diphtheria, and pertussis, for which booster doses are required to achieve protective Ab levels (72), which is achieved sometimes after 4–6 mo of life. The causal agent of tetanus is *Clostridium tetani*, an anaerobic bacterium. *C. tetani* releases a neurotoxin that causes prolonged muscular contractions. Maternal and neonatal tetanus was a common life-threatening infection as a result of unclean delivery and umbilical care practices. The implementation of maternal immunization to protect against neonatal tetanus in the 1960s has resulted in a 92% decrease in neonatal tetanus mortality rates worldwide (2). Routine vaccination has also led to the near eradication of diphtheria, an upper respiratory infection caused by *Corynebacterium diphtheria*, in the United States (73).

In contrast with tetanus and diphtheria, pertussis, a respiratory infection caused by *Bordetella pertussis*, continues to be an important risk concern despite the availability of a vaccine (74, 75). Pertussis-related morbidity and mortality disproportionately affect young infants (74, 76, 77), and a significant decrease in pertussis-related hospitalization only occurs after the administration of two vaccine doses (78). As the current vaccine schedule recommends Tdap vaccination at 2 mo of age with booster doses,
at 4, 6, 15, and 18 mo, then between 4 and 6 y of age, infants <4 mo of age are particularly vulnerable to infection. In a randomized trial, the addition of a vaccine dose at 14 d of life was associated with lower Ab responses, raising concerns about vaccine efficacy (79). Thus, protection of infants in the first months of life heavily depends on maternally acquired Abs. Consequently, the World Health Organization recommends that national programs consider vaccination of pregnant women with a dose of Tdap in addition to infant pertussis immunization in countries with high pertussis-related infant morbidity/mortality (80). In the United States in 2011, the Advisory Committee on Immunization Practices recommended Tdap immunization of unvaccinated pregnant women to protect young infants from pertussis (81). This recommendation was updated in 2012 to extend Tdap immunization to all pregnant women in every pregnancy (82). Recent reports have demonstrated that maternal vaccination is effective to prevent infant pertussis, especially during the first 2 mo of life (83).

**Vaccines currently under research for the prevention of neonatal infections**

Although vaccines such as influenza and Tdap significantly contribute to reducing neonatal infections, these vaccines were not specifically developed to target pregnant women. Nevertheless, some maternal vaccines specifically aimed at fetal-infant immunization are at different stages of research and development.

**Streptococcus agalactiae (GBS).** Infant GBS infection can result in early-onset (during the first week of life) or late-onset disease (8–90 d of life). Intrapartum antibiotic prophylaxis to colonized mothers has reduced the incidence of early-onset neonatal GBS but had little impact on late-onset disease in the United States (84). Importantly, screening and treatment of all colonized pregnant women is not feasible in the developing world where GBS is a significant contributor to neonatal mortality. A maternal vaccine could therefore help reduce the burden of neonatal disease, as well as potentially impact adverse pregnancy outcomes associated with GBS such as miscarriage, preterm birth, and premature rupture of membranes. In fact, a recent study has indicated that a maternal GBS vaccine could be a cost-effective intervention in low-income countries, especially in areas with high case fatality rates (85). A trivalent conjugate vaccine containing serotype Ia, Ib, and III was found to be safe and immunogenic in phase 1 and 2 clinical trials (86, 87). Although the serotypes included in this vaccine are representative of the predominant serotypes in Europe and America, other serotypes also contribute the neonatal infections in other areas of the world (88). Thus, the impact of this vaccine in parts of the world where GBS serotypes not included in the vaccine are prevalent may be limited. A multivalent GBS vaccine is currently tested for safety and immunogenicity in a phase 1/2 trial in healthy nonpregnant adults (clinicaltrials.gov number NCT03170609) and is planned for testing in pregnant women.

**Respiratory syncytial virus.** RSV is the leading cause of viral acute lower respiratory tract infections, and it is estimated that in the United States, 60% of infants will be infected during their first RSV season. RSV infection is particularly severe in preterm infants (89). An mAb (palivizumab) is administered to infants at high risk for severe disease in many developed countries, but this approach can be cost prohibitive. A formalin-inactivated vaccine developed in the 1960s was associated with enhanced disease among vaccinated children, slowing vaccine development for several years. Vaccine studies in infants <6 mo with novel vaccine candidates have generally demonstrated poor immunogenicity (90). A maternal vaccine would therefore be ideal to protect neonates and infants. The development of a maternal vaccine is notably supported by the association between high levels of maternal Abs with less severe disease (91), as well by the protection conferred by passive immunization with palivizumab. In addition, maternal immunization would allow bypassing the safety concern associated with RSV vaccination in infants (92). To this end, an F protein nanoparticle maternal vaccine is currently evaluated in phase 3 clinical trials (clinicaltrials.gov number NCT02624947).

**Unmet needs for maternal vaccines**

Maternal vaccination could also be important for the prevention of other vertically transmitted infections, such as HIV and CMV.

**Maternal HIV vaccines.** Despite the wide availability and high efficacy of maternal antiretroviral medication, >150,000 infants worldwide continue to acquire HIV in the prenatal and postnatal period, and the risk for an HIV-exposed infant becoming infected can be as high as 14% in some regions (93). One of the highest risk settings is a new diagnosis or acquisition of HIV during pregnancy, where initiation of antiretroviral medications during pregnancy is associated with high risk for vertical virus transmission (94). Thus, strategies that can synergize with maternal antiretroviral medication are needed to eliminate the pediatric HIV epidemic. One possible strategy is the development of a maternal vaccine that can elicit maternal immunity that can block HIV transmission to the infant. As the infant acquires maternal IgG via the placenta throughout pregnancy, infant transmission has the unique characteristic of occurring in the setting of Abs that were induced by the autologous virus strain present in the HIV-exposed host. The role of maternal Abs in defining the risk for virus transmission from mother to child transmission has been extensively studied, and variable conclusions have been reached on the protective nature of maternal Abs, depending on the population studied (95). Yet, all modes of infant transmission are consistently associated with a strict viral genetic bottleneck, similar to that of heterosexual transmission, in which a single or small number of transmitted/founder maternal viruses initiate infection in the infant (96–100). Moreover, evidence exists that the resistance to autologous virus neutralizing Abs may be responsible for the selection of infant-transmitted variants (101–105). Thus, there is the potential that enhancement of the mother’s ability to neutralize her own autologous virus variants could contribute to reducing the risk for infant transmission. Interestingly, common HIV envelope-specific Abs that are readily induced by current generation HIV vaccines, such as variable loop 3 and CD4 binding site–specific Abs that demonstrate neutralization potency against only tier 1 “easy
to neutralize heterologous virus variants, have recently been established to have autologous neutralizing activity (106, 107). The ability of these easy-to-induce Abs to neutralize autologous virus suggests that current HIV vaccines administered to HIV-infected pregnant women could play a role in further reducing vertical virus transmission. Work to model this strategy of employing HIV envelope vaccines to enhance autologous virus neutralizing activity that could block vertical virus transmission is ongoing in nonhuman primate (NHP) models.

**Maternal CMV vaccines.** Congenital CMV is the leading infectious cause of infant brain damage and permanent disabilities worldwide. Nearly 1% of all infants are born with congenital CMV, and at least 20% of those infected infants will go onto have life-long disabilities, most commonly, hearing loss (108). Moreover, up to a quarter of infant hearing loss is attributable to congenital CMV infection. The annual impact of congenital CMV in the United States alone has been estimated to be $4 billion. Thus, a vaccine to eliminate congenital CMV transmission is of highest public health priority, and was named a top tier priority vaccine by the National Academy of Medicine 15 y ago (109). Yet, few CMV vaccines have moved into late-phase clinical trials. One complicating factor is that although primary CMV infection of the mother is the highest risk for congenital transmission, CMV can be placently transmitted in the setting of natural maternal immunity. Yet, the risk for CMV transmission to the fetus after maternal reinfection in the setting of pre-existing maternal immunity is considerably lower than that of primary maternal infection (110, 111). Thus, a vaccine that is fully protective against congenital transmission must elicit immunity that is distinct from or improves on natural CMV immunity. Although a CMV vaccine would be most effective against congenital CMV infection if administered universally before childbearing years, one possible strategy is to provide temporary passive or active immunity to women who remain without potentially protective CMV immunity during pregnancy to ameliorate the high risk for transmission in the setting of primary maternal infection. In fact, a recent study in the NHP model of congenital CMV transmission demonstrated that passive infusion of polyclonal anti-CMV Abs before maternal virus challenge was protective against placental virus transmission (112). Although clear immune correlates of protection against HCMV acquisition in humans are not yet known, in a recent phase 1 clinical trial, a replication-incompetent CMV vaccine (V160) was demonstrated to be safe and induced neutralizing Abs and cell-mediated responses in healthy seronegative adults (clinicaltrials.gov number NCT01986010). More studies in both healthy adults and pregnant populations are needed to evaluate the role of CMV vaccine-elicited neutralizing Abs and cell-mediated responses. Furthermore, a better understanding of maternal immune correlates of transmission risk in the setting of pre-existing immunity could direct maternal vaccine development to enhance the identified protective response during pregnancy. Thus, maternal vaccination for CMV may be an effective strategy to temporally improve the mother’s ability to block congenital CMV transmission upon CMV exposure.

**Maternal Zika virus (ZIKV) vaccine.** ZIKV is a mosquito-borne flavivirus that was first discovered in Africa in the 1940s and was previously associated with mild disease, with no known pregnancy-related complications. As of March 2017, >80 countries have reported evidence of ZIKV transmission (113) and in recent years, ZIKV infection has been associated with several complications, including neurologic defects in infants born to ZIKV-infected women (114). Several ZIKV vaccine candidates using different platforms have shown promising results in preclinical studies. A purified inactivated virus vaccine derived from a Puerto Rican strain was shown to induce ZIKV-specific neutralizing Abs and protect from virus challenge in mice and NHP models (115), and DNA vaccines encoding the prM/E genes of ZIKV elicited strong binding and neutralizing Abs in rhesus monkeys (116, 117). In addition, an mRNA vaccine encoding the prM and E genes of a French Polynesian strain induced strong CD4+ T cell and neutralizing Ab responses in nonpregnant mice and protected mice and NHPs from virus challenge (118). Importantly, it was recently reported that an inactivated virus vaccine was safe in humans and elicited neutralizing Ab responses that were higher than the protective threshold observed in animal studies (119). Several additional clinical trials testing different vaccine platforms including inactivated virus, DNA, mRNA, virus vector, and synthetic peptide vaccines are ongoing. It is worth noting that although congenital ZIKV infection is a major public health concern, none of these vaccine platforms specifically target pregnant women. Designing ethical clinical trials that include pregnant women may be warranted for the eradication of mother-to-child transmission of ZIKV.

**Importance of timing of maternal vaccination**

Multiple factors need to be considered when determining the timing of maternal immunization. These include whether the goal is to protect mothers, infants, or both; the kinetics of maternal response to vaccination; the efficiency and timing of IgG transfer; and the half-life of Abs. Thus, the timing of maternal vaccination for optimal Ab levels in infants at birth may vary between vaccines. For example, transfer of *H. influenzae* type B-specific Abs is greater when women are immunized at least 1 mo before delivery (62). Moreover, the concentration and the avidity of pertussis toxin–specific Abs in the cord blood are higher when mothers are immunized during the second trimester (120) or early in the third trimester of gestation (121) as compared with mothers immunized later in the third trimester. Similarly, the proportion of preterm and full-term babies with protective levels of anti-pertussis Abs at birth is higher when mothers are immunized during the second trimester of gestation (120, 122). It was also previously demonstrated that the transplacental transfer of maternal pertussis-specific IgG is higher in women immunized during pregnancy (123) than in those immunized before pregnancy. Nevertheless, these maternal Abs rapidly wane; thus, it is estimated that by 2 mo of age only 41% of infants have detectable levels of pertussis-specific IgG (123). Matching the peak immune response after maternal vaccination and the peak IgG transplacental transport may result in high IgG transfer efficiency in full-term babies.
babies, but protection of premature babies may require maternal immunization early in pregnancy. Thus, the infant target population (full-term babies versus all viable babies) should be carefully considered when developing maternal immunization strategies.

**IMPACT OF IgG TRANSPLACENTAL TRANSFER ON INFANT IMMUNITY**

**Early life vaccination**
Because of the high vulnerability of infants to infections, the first months of life constitute a critical window for the generation of protection immunity via vaccination. Vaccination in early life is unique in that occurs: 1) in the setting of an immune system transitioning from an environment in which the fetus is exposed to a limited set of Ags including the placental microbiome to exposure to a wide variety of Ags from the external world, and 2) in the presence of maternally acquired Abs. Only a few vaccines are administered to neonates at birth, and the majority of vaccines administered during the first months of life are initiated at 6–8 wk of life (124). These vaccines usually require booster doses to induce high-magnitude, durable responses (72). Importantly, recent studies have highlighted the importance of adjuvants for inducing robust durable immune responses in early life (125). Moreover, some studies have indicated that immunization in early life can induce more durable Ab responses than in adults (126, 127).

**Interference of maternal Abs with infant vaccine responses**
Although maternal Abs transferred across the placenta are important to protect infants during the first months of life, several reports have indicated that maternal Abs interfere with the development of infant immune responses. One of the best studied examples of maternal Ab impact on infant immune response is the measles vaccine. In fact, several studies have demonstrated that infant immunization in the presence of maternal Abs leads to poor Ab responses (reviewed in Ref. 128). Nevertheless, maternal Abs do not interfere with the induction of measles-specific T cell responses (129). Moreover, infant immunization in the presence of maternal Abs leads to B cell priming as enhanced immune responses are observed after a booster dose of vaccine (130). To assess the impact of maternal Abs on vaccine commonly administered in infancy, Jones et al. (131) examined the relationship between the concentration of Abs against pertussis, *H. influenzae* type B, tetanus toxoid, and pneumococcal Ags at birth and after primary immunization. High concentrations of Ab at birth were associated with lower postimmunization titers for tetanus and pneumococcus, but this association was not observed with *H. influenzae* type B or pertussis. Importantly, despite maternal interference, most infants achieved protective levels of Abs following vaccination. Previous studies have also indicated that maternal Abs did not suppress infant Ab responses to *H. influenzae* type B vaccines (132). Similarly, it was recently reported that maternal levels of HIV-specific Abs do not prevent the development of HIV vaccine–elicited Abs in HIV-exposed infants (126). Importantly, animal studies have indicated that the effects of maternal Abs can last even after waning because maternal Abs can shape the B cell repertoire of the offspring (133). Several mechanisms have been hypothesized to explain how maternal Abs inhibit infant responses. These include: 1) live viral vaccine neutralization by maternal Abs, 2) Ab feedback mechanisms, 3) elimination of vaccine-antigen/maternal Ab immune complexes by phagocytosis, 4) inhibition of B cell responses through epitope masking, and 5) inhibition of B cell responses by binding of IgG to the FcγRIIB (134, 135). A better understanding of how maternal Abs interfere with the infant immune system is key to developing combined maternal and infant immunization strategies that will ensure the continuous protection of infants.

**Impact of mAb biologics administered during pregnancy on the fetus**
As the number of effective mAb biologics for treatment of immune-mediated diseases and cancer is on the rise and although typically contraindicated in pregnancy, these highly effective therapies are often needed to treat maternal disease during pregnancy. Thus, the safety of these products for fetal development has become an important question. The majority of Ab therapeutics are IgG isotype and contain Fc regions that can interact with FcRn, and thus can be transferred across the placenta to the fetal circulation. Therefore, there is a risk for fetal effects from the maternal treatments. In fact, fetal effects of maternal mAb biologic treatment have been reported: infants exposed to maternal rituximab, an anti-CD20 mAb, have been reported to have low B cell numbers, circulating IgG levels (136, 137), and potential infection complications (136, 138). Moreover, the impact of modifications of the Fc receptor binding site that have successfully prolonged the half-life of mAb biologics on placental transfer risk is unknown. Therefore, a better understanding of the mechanisms of IgG transfers across all cell layers of the placenta are highly needed to inform the design of biologics that can effectively treat maternal disease, but avoid transfer across the placenta.

**CONCLUSIONS**
The transfer of IgG from mother to fetus across the placenta is critical to protect infants during the first few months of life. This transfer can be improved through maternal vaccination during pregnancy, and the timing of vaccination is critical to provide adequate protection to both mother and infant. Importantly, maternal immunization could also have deleterious effects on the neonate or young infant. A better understanding of the mechanisms of IgG transfers across all cell layers of the placenta is highly needed to: 1) inform the design of biologics that can safety be administered to pregnant women with limited impact on the fetus/infant; and 2) optimize maternal immunization regimens to protect infants during the first months of life.
DISCLOSURES

G.K.S. is on a Data and Safety Monitoring Board for a GlaxoSmithKline-funded RSV vaccine study in pregnant women. She has received research funding for studies of GBS vaccine in pregnant women produced by Novartis, for RSV vaccine in pregnant women produced by Novavax, and for RSV mAb in late preterm infants produced by Regeneron. S.R.P. is a consultant for Pfizer vaccines and has a sponsored program on preclinical vaccine development with Merck. The other authors have no financial conflicts of interest.

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