Human Reproduction Update, Vol.21, No.1 pp. 119–135, 2015
Advanced Access publication on July 11, 2014 doi:10.1093/humupd/dmu041

human reproduction update

Maternal vaccination: moving the science forward

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Submitted on March 23, 2014; resubmitted on May 28, 2014; accepted on June 13, 2014

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BACKGROUND: Infections remain one of the leading causes of morbidity in pregnant women and newborns, with vaccine-preventable infections contributing significantly to the burden of disease. In the past decade, maternal vaccination has emerged as a promising public health strategy to prevent and combat maternal, fetal and neonatal infections. Despite a number of universally recommended maternal vaccines, the development and evaluation of safe and effective maternal vaccines and their wide acceptance are hampered by the lack of thorough understanding of the efficacy and safety in the pregnant women and the offspring.

METHODS: An outline was synthesized based on the current status and major gaps in the knowledge of maternal vaccination. A systematic literature search in PUBMED was undertaken using the key words in each section title of the outline to retrieve articles relevant to pregnancy.

Articles cited were selected based on relevance and quality. On the basis of the reviewed information, a perspective on the future directions of maternal vaccination research was formulated.

RESULTS: Maternal vaccination can generate active immune protection in the mother and elicit systemic immunoglobulin G (IgG) and mucosal IgG, IgA and IgM responses to confer neonatal protection. The maternal immune system undergoes significant modulation during pregnancy, which influences responsiveness to vaccines. Significant gaps exist in our knowledge of the efficacy and safety of maternal vaccines, and no maternal vaccines against a large number of old and emerging pathogens are available. Public acceptance of maternal vaccination has been low.

CONCLUSIONS: To tackle the scientific challenges of maternal vaccination and to provide the public with informed vaccination choices, scientists and clinicians in different disciplines must work closely and have a mechanistic understanding of the systemic, reproductive and mammary mucosal immune responses to vaccines. The use of animal models should be coupled with human studies in an iterative manner for maternal vaccine experimentation, evaluation and optimization. Systems biology approaches should be adopted to improve the speed, accuracy and safety of maternal vaccine targeting.

Key words: pregnancy / vaccine / immunology / antibody / animal model

Introduction

Immunization has played a crucial role in eliminating or reducing the occurrence of devastating infections worldwide (Roush *et al.*, 2007; Andre *et al.*, 2008). Maternal vaccination, a form of immunization for women of childbearing age before, during or after pregnancy, aims at protecting the mother against infections that may threaten healthy reproduction and allowing vaccine-induced maternal antibodies to be transferred via placenta to the fetus and in colostrum and breast milk to the infant for protection against diseases before routine childhood immunization can be initiated. The protection function of maternal vaccination in neonates was initially suggested by a correlation between a maternal deficiency of Group B streptococcus (GBS) anti-capsular antibodies and neonatal susceptibility to invasive GBS infection (Baker and Kasper, 1976). Because of the potential of protecting the mother and the fetus as well as the newborn and the advantage of circumventing the challenges of inducing efficient protective immunity in neonates, maternal vaccination has now emerged as a recommended public health approach against maternal and childhood infections.

In spite of the success of several maternal vaccines, many gaps exist in our knowledge of this promising public health strategy. All current maternal vaccine formulations were initially designed for and tested in non-pregnant populations, but the diverse immune modulations during pregnancy may cause pregnant women to respond sub-optimally or differently compared with non-pregnant populations. Efficacy is further affected by a plethora of other variables, such as the form, dose, route and timing of the vaccination. Very limited data exist on the effect in populations of high-risk pregnancies, such as recurrent miscarriage, pre-eclampsia, autoimmunity and immunodeficiency. Many recommended maternal vaccines are completely lacking in systematic surveillance data on their safety. A long list of pathogens have no available vaccines or vaccines that are contraindicated for pregnancy. By integrating the current status of major medical concerns over maternal vaccination, the recent advances in pregnancy-associated humoral immune modulation that may influence vaccine responsiveness and a discussion on the animal models for maternal vaccination development, this review aims to bridge the gaps in the literature, offer a mechanistic direction for maternal vaccine research and encourage basic, clinical and translational scientists to work together toward developing effective and safe maternal vaccines.

Methods

We first synthesized an outline of the review based on the current recommendations and major gaps in the knowledge of maternal vaccination. Following the outline, a systematic literature search was performed in PUBMED using the key words in each section title of the outline to retrieve articles relevant to pregnancy and published in English up to March 2014. The search was performed without limitations by species, but the species involved in the cited studies were indicated in the text when necessary. Relevant abstracts from recent scientific meetings were also included. Articles cited were selected based on relevance and quality as interpreted by all the authors. No quantitative or statistical analysis was performed. On the basis of the reviewed information and the recent progress in vaccinology and reproductive immunology, we formulated a perspective on the future directions of maternal vaccination research.

Rationales of maternal vaccination

Fetal and neonatal susceptibility to infections

A major rationale for vaccinating the mother during pregnancy is that neonates do not mount efficient protective immunity to many viral, bacterial and fungal pathogens and are prone to more severe or prolonged infections than adults (Silverstein, 1964; Darmstadt *et al.*, 2011). The increased neonatal susceptibility to infections is more pronounced in infants born prematurely (Stoll *et al.*, 2002; Stoll and Hansen, 2003). Therefore, by vaccinating the mother, humoral immunity can be passively transferred to the fetus and the newborn. Historically, the susceptibility of the fetus to infections was believed to be due to the immaturity of the fetal immune system (Billingham *et al.*, 1953) and its tendency to mount tolerogenic responses to antigens (Silverstein, 1964). The heightened neonatal susceptibility was attributed to a less intact mucosal barrier and the lack of existing immunological memory as well as the immaturity of the neonatal immune system, being incapable of developing adult-like protective immune responses (Adkins *et al.*, 2004; Levy, 2007). Lending credence to this historical notion, many quantitative and qualitative differences in both the innate and the adaptive components of fetal and neonatal immune systems from their adult counterparts were documented (Garcia *et al.*, 2000; Adkins *et al.*, 2004; Levy, 2007; Siegrist and Aspinall, 2009). Of note, fetal and neonatal T cells were found to

deviate toward the development of regulatory T cell (T_{reg}) or T helper type 2 (T_H2) responses that are ineffective in protection against intracellular pathogens (Adkins *et al.*, 2004; Michaelsson *et al.*, 2006; Wang *et al.*, 2010). The antibody responses to many encapsulated bacteria (such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*), which are the leading causes of bacterial infections in infants, and their polysaccharide antigens are weak in early infancy. This is perhaps due to delayed formation of the splenic marginal zone (MZ) (MacLennan *et al.*, 1985; Timens *et al.*, 1989) that harbors MZ B cells producing polysaccharide-reactive antibodies (Cerutti *et al.*, 2013) and reduced expression of activating receptors on neonatal B cells (Timens *et al.*, 1989; Kaur *et al.*, 2007; Kanswal *et al.*, 2008).

Recent studies have argued against the fetal immune system being immature versions of the adult immune system (Mold *et al.*, 2010). In addition, a series of studies have showed that the neonatal immune system can harbor considerable plasticity, and the intrinsic differences in neonatal immune cells from their adult counterparts can be overcome by appropriate manipulation of the neonatal immune environment to generate adult-like T_H1, cytotoxic T lymphocyte (CTL) and humoral responses (Forsthuber *et al.*, 1996; Ridge *et al.*, 1996; Sarzotti *et al.*, 1996; Hassett *et al.*, 1997; Martinez *et al.*, 1997; Bot *et al.*, 1998; Brazolot Millan *et al.*, 1998; Jakobsen *et al.*, 1999; Franchini *et al.*, 2001; Kovarik *et al.*, 2001; Fadel *et al.*, 2002; Wynn *et al.*, 2008). These observations have engendered much effort in the design of vaccine formulations and protocols to stimulate neonatal immunity (Wood and Siegrist, 2011), although with limited success. Neonatal vaccination should be pursued but with caution. Many agents designed to break neonatal tolerance and induce vaccine responsiveness may trigger side effects, such as pathological inflammation or toxicity, which are deleterious to development (Kovarik *et al.*, 2000). Furthermore, recent progress in our understanding of the immunologic challenges during prenatal life and the transition from fetal to neonatal life has revealed important physiologic significance to this attenuated perinatal immunity. The deviation toward an anti-inflammatory T_H2 or T_{reg} response during mid-to-late gestation may protect the fetus from preterm delivery or other unwanted pregnancy complications that could otherwise occur in a pro-inflammatory T_H1 or T_H17 milieu (Vitoratos *et al.*, 2006; Ito *et al.*, 2010), and compromised neonatal immunity may limit detrimental inflammation during mucosal colonization by commensal microbes shortly after birth (Lotz *et al.*, 2006; Elahi *et al.*, 2013). These potential hurdles to neonatal vaccination, coupled with the concern that infection can precede the development of a vaccine response, make maternal vaccination an appealing alternative strategy to induce immune protection in neonates.

Maternal susceptibility to infections

Similar to neonates, epidemiological data have shown that pregnant women have an increased incidence of and/or severity to a variety of infections, such as influenza, varicella, measles, severe acute respiratory syndrome, tuberculosis, listeriosis, pneumocystis, toxoplasmosis and malaria (Jamieson *et al.*, 2006; Pazos *et al.*, 2012a; Sappenfield *et al.*, 2013). These observations have given rise to the theory that pregnancy represents an immunocompromised state associated with inefficient pathogen control. Further supporting this theory is the apparent immunological challenge women face during pregnancy, i.e. to be tolerant to the semi-allogeneic fetus, which requires maternal suppressive immune modulations. However, a careful examination of the epidemiological data suggests that the severity of infections varies at different stages of pregnancy. For example, the severity of *Plasmodium falciparum* malaria and of toxoplasmosis were found in some studies to be the highest during the first half of pregnancy and to decline gradually as pregnancy proceeded (Bray and Anderson, 1979; Jenum *et al.*, 1998; Okoko *et al.*, 2003), while women in the second and third trimesters were shown to have higher maternal and fetal mortality and morbidity from influenza A infection (Lindsay *et al.*, 2006, Neuzil *et al.*, 1998; Schanzer *et al.*, 2007; Siston *et al.*, 2010) and a higher incidence of *Listeria monocytogenes* (Gellin *et al.*, 1991; Benshushan *et al.*, 2002; Mylonakis *et al.*, 2002). Such differences are likely to result from the distinct types of protective immunity required to control the various pathogens during acute or chronic infection and the unique immunological alterations occurring at different stages of pregnancy, both systemically and at the maternal-fetal interface. During early pregnancy when implantation and placentation take place, extensive tissue remodeling triggers a maternal local inflammatory immune reaction. During the second and third trimesters, the dramatic tissue remodeling subsides and rapid fetal growth occurs, which entails the mother and the developing conceptus co-existing peacefully in an anti-inflammatory environment in order to avoid fetal rejection. Toward the final phase of pregnancy when fetal development is complete, an inflammatory process takes places in the uterus to activate smooth muscle contraction and parturition ensues. Therefore, it would be conceivable that the higher severity of the mother and the fetus to certain placental parasitic infections, such as *P. falciparum* malaria and toxoplasmosis, during early pregnancy may reflect dominant local pro-inflammatory T_H1 and T_H17 immune responses that amplify collateral tissue damage (Fievet *et al.*, 2001; Ge *et al.*, 2008; Goldszmid and Trinchieri, 2012), while the higher severity to influenza A and *L. monocytogenes* during the second trimester may reflect diminished systemic and local T_H1 immunity that is critical for protection (Barber *et al.*, 2005). The complex spatial and temporal host-pathogen interaction during pregnancy dictates that the biology of the pathogen, the timing of vaccination as well as the effect of the vaccine on both maternal systemic and reproductive mucosal immune systems should be examined when designing maternal vaccine formulations and protocols that will be effective and safe for the mother and the fetus.

Principles of maternal vaccination

Maternal vaccination generates active innate, humoral and cell-mediated immune protection in the mother to increase resistance against infections and reduce the chance of vertical transmission of infections to the fetus (Fig. 1A, left). In addition, maternal vaccination elicits systemic immunoglobulin G (IgG) antibodies that can be transferred to the fetus via the placenta in humans (Fig. 1A, middle and right) and mucosal IgG, IgA and IgM antibodies that are secreted into the colostrum and milk and ingested by the newborn during breastfeeding (Fig. 1B) to confer immune protection. Species vary in the contribution each route makes to the transfer of immunity. In humans and mice, maternal antibodies can be transferred via both routes (Renegar, 2005).

Maternal immune protection

The argument for vaccination in pregnancy is not solely based on altruistic behavior on the part of the mother. As noted above, women who are pregnant remain at risk for a variety of vaccine-preventable diseases.

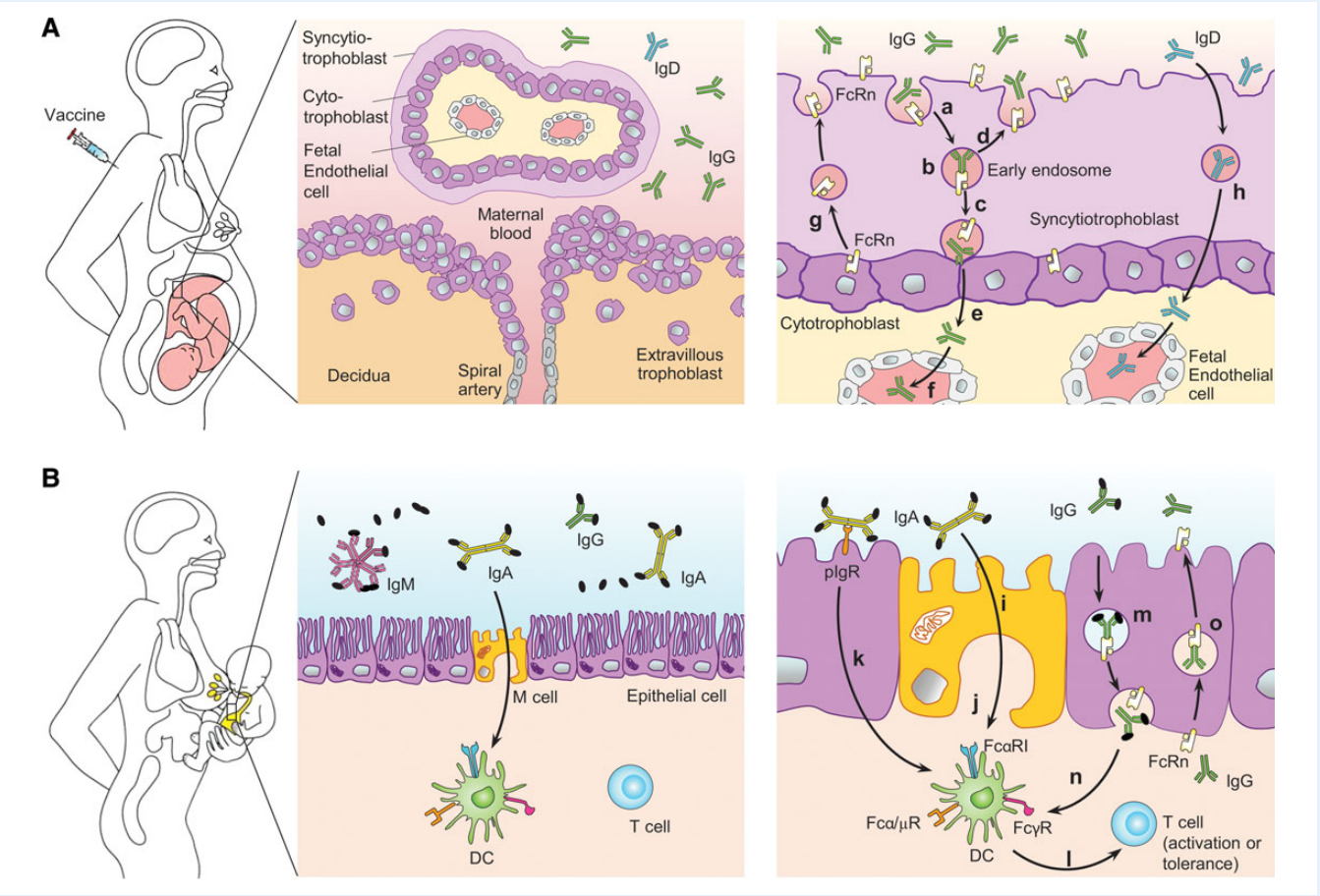

Figure 1 Mechanisms of vaccine-induced maternal, fetal and neonatal immune protection. (**A**) Maternal vaccination induces innate, humoral and cell-mediated immunity that confers direct protection of the mother against infections (left panel). Vaccine-induced maternal IgG is also transferred to the fetus to confer systemic passive immunity (middle and right panels). Maternal IgG is endocytosed into villous syncytiotrophoblasts from the maternal surface (a) and binds to FcRn in the acidic environment of early endosomes (b). IgG-FcRn complexes are then either transcytosed to the fetal side of syncytiotrophoblasts (c) or recycled back to the maternal side (d). IgG dissociates from FcRn upon exposure to the neutral pH environment at the fetal side of syncytiotrophoblasts (e) and enters fetal circulation (f). FcRn on the fetal side of syncytiotrophoblasts can be retrieved back to the maternal side to participate in subsequent IgG transport (g). Maternal vaccine-induced IgD could cross trophoblasts and enter fetal circulation via an unknown mechanism (h). (**B**) Maternal vaccination-induced antibodies, including IgA, IgG, IgM and IgD, are also secreted into colostrum and milk. During breastfeeding, these antibodies are ingested by the neonate (left panel). IgA, IgG and IgM confer neonatal mucosal immune protection by binding to commensal and pathogenic microbes and their virulence factors to mediate immune exclusion and neutralization (middle panel). In addition, maternal IgA facilitates antigen sampling in the neonatal intestinal mucosa by crossing M cells via an unknown receptor (i) or apical-to-basolateral retro-transcytosis via polymeric Ig receptor (pIgR) (k). Besides delivering antigens to mucosal dendritic cells (DCs), IgA can interact with DCs via FcαRI, leading to either immunity against pathogenic microbes or tolerance to commensal microbes (l). IgA can also interact with Fcα/μR on DCs to mediate immune tolerance. Ingested maternal IgG can also cross epithelial cells via FcRn (m) through a mechanism similar to that in syncytiotrophoblasts. This pathway delivers antigens to, and regulates, DCs via activating or inhibitory FcγRs (n). Maternal IgG acquired during the perinatal period can be re-secreted by FcRn into the lumen to participate in mucosal immune defense (o).

These infectious processes result in identifiable morbidity and mortality in the mother, and the associated adverse host systemic responses can lead to disruptions in physiologic homeostasis thus compromising the co-existing fetus. Despite these rather obvious observations, few data exist examining the maternal and fetal benefits of vaccination. This is perhaps due to a general unwillingness to study the pregnant patients, which requires a reassessment of strategies (Brent, 2003; Healy, 2012). Most of the available literature on maternal immune protection by vaccination relates to influenza infection. A large cohort study demonstrated significant reduction in maternal flu-like disease in those vaccinated in pregnancy (Zaman *et al.*, 2008). Of additional interest, the neonates from the pregnant mothers who were vaccinated also showed a significant reduction in influenza and flu-like respiratory disease after delivery.

Neonatal systemic immune protection

Significant placental transfer is found for maternal IgG. After endocytosis by placental syncytiotrophoblasts, maternal IgG binds to neonatal Fc receptor (FcRn) in the acidic environment of early endosomes. FcRn-IgG

complexes are then transported to the fetal surface of the syncytiotrophoblasts, where the neutral pH promotes IgG dissociation. IgG subsequently passes through the villous stroma and fetal capillary endothelium and enters fetal circulation. The amount of IgG transferred is a function of maternal IgG concentration, IgG subclass, the level of FcRn expression on syncytiotrophoblasts and gestational age. Preferential transport was found for IgG_1 and IgG_4 over IgG_3 and IgG_2 (Costa-Carvalho *et al.*, 1996). Vaccines that contain protein antigens, such as Tdap, elicit a predominantly IgG_1 and IgG_3 response, which is transferred more efficiently than polysaccharide vaccine antigens, which predominantly elicit an IgG_2 response (van den Berg *et al.*, 2010). IgG transfer can begin as early as 13 weeks of gestation and occurs as pregnancy proceeds, with the largest amount transferred in the third trimester (Saji *et al.*, 1999). The fetal IgG concentration usually exceeds that in the maternal circulation at full term, consistent with placental IgG transfer as an active transport process. A sharp increase of maternal IgG in cord blood occurs after 36 weeks of gestation, and this has prompted the Advisory Committee on Immunization Practices (ACIP) to recommend that the optimal timing of Tdap vaccination is the third trimester, which would provide the highest concentration of maternal antibodies in the fetus at birth (Centers for Disease Control and Prevention, 2013b; Healy *et al.*, 2013). However, a study on influenza vaccination found that first trimester vaccination could also improve fetal and neonatal outcomes by reducing the rate of stillbirth (Sheffield *et al.*, 2012). Evidence supporting impaired placental IgG transfer in mothers infected with human immunodeficiency virus-1 (HIV-1) or malaria and in babies born at term with lower birthweight has been found (Wesumperuma *et al.*, 1999; Okoko *et al.*, 2002), highlighting the need for careful design and evaluation of maternal vaccines in mothers with existing infections or other underlying conditions.

Neonatal mucosal immunity and tolerance

Maternal non-specific and specific antibodies elicited by vaccination, including IgA, IgM and IgG, are secreted into colostrum and milk. After ingestion by the neonates during breastfeeding, they provide mucosal immune protection by inhibiting commensal and pathogen adhesion and invasion and by promoting exclusion and neutralization. Secretory IgA is the predominant antibody class in human colostrum and milk (Mickleson and Moriarty, 1982; Telemo and Hanson, 1996), while IgG is the most abundant antibody class in mouse milk (Ijaz *et al.*, 1987). In the gut, ingested maternal IgA can undergo retrograde transport across M cells via an unknown receptor (Mantis *et al.*, 2002) or across duodenal epithelial cells via the transferrin receptor (CD71) (Cerutti and Rescigno, 2008). Ingested maternal IgG can also undergo retrograde transport by FcRn expressed on the apical surface of intestinal epithelial cells (Israel *et al.*, 1995). These mechanisms can promote the induction of immunity against luminal pathogens and tolerance to commensal microbes (Oda *et al.*, 1983; Kohl and Loo, 1984; Heiman and Weisman, 1989; Yoshida *et al.*, 2004, 2006; Favre *et al.*, 2005). Intestinal FcRn can also mediate the resecretion of maternal IgG previously acquired via placental transfer during prenatal life and control luminal pathogens (Harris *et al.*, 2006).

Developing a better understanding of IgD

Whereas much of the attention on maternal vaccination has been focused on vaccine-induced maternal antepartum IgG response and post-partum IgG, IgA and IgM responses in breast milk, IgD, an enigmatic member of the immunoglobulin family, has been left in oblivion. However, many features of IgD make it an appealing target of maternal vaccination. IgD is enriched in the upper respiratory mucosa, markedly increased in patients with selective IgA deficiency (Chen and Cerutti, 2010a) and contributes to immune defense against respiratory pathogens such as *H. influenzae* and *Moraxella catarrhalis* that are common neonatal infections (Chen *et al.*, 2009). Maternal rubella-specific IgD persists longer than IgM and IgA after infection, and significant amounts of rubella-specific IgD can be transferred across the placenta during pregnancy, albeit through an unknown mechanism (Fig. 1A, right), allowing cord blood rubella-specific IgD levels to reach levels comparable to those in maternal blood (Salonen *et al.*, 1985). IgD is also present in human amniotic fluid and is concentrated in milk (Cederqvist *et al.*, 1978; Sewell *et al.*, 1979; Steele and Leslie, 1985; Litwin *et al.*, 1990), which may provide fetal and neonatal immune protection. Furthermore, secreted IgD exhibits extensive V(D)J gene somatic hypermutation and has a long, protruding, finger-like heavy chain complementarity determining region 3 (Koelsch *et al.*, 2007), which may be key to the neutralization of highly conserved bacterial and viral epitopes with recessed topography (Saphire *et al.*, 2001; Burton *et al.*, 2005). IgD can also monitor the presence of systemic pathogens by activating the antimicrobial, antibody-inducing and pro-inflammatory functions of basophils (Chen *et al.*, 2009). The production of IgD is positively regulated by T_H2 cytokines (Levan-Petit *et al.*, 1999), allowing IgD-inducing vaccines to be more compatible with pregnancy than vaccines whose induction and protection require a strong pro-inflammatory T_H1 environment. Finally, IgD inhibits IgE-induced histamine release but not cytokine production by basophils (Cerutti and Chen, 2010) and thus may be targeted by maternal vaccination to control the rising rate childhood allergies without triggering adverse pregnancy outcomes associated with histamine, such as preterm labor, pre-eclampsia and spontaneous abortion (Bytautiene *et al.*, 2004; Brew and Sullivan, 2006). However, IgD has been neglected for a long time, and there has been no study on the function of IgD in maternal, fetal or neonatal protection at the time of this review.

Current maternal vaccine recommendations, use and safety

General guidelines

All guidelines considered today for maternal vaccination during pregnancy in the USA are derived from the ACIP. Currently, the ACIP committee has found no evidence of risk to the fetus from maternal vaccination from dead, inactivated or toxoid sources (National Center for Immunization and Respiratory Diseases, 2011). For live vaccines, there have been few conclusive studies. As a result, attenuated viral or live bacterial vaccines are routinely avoided unless there is a high risk of exposure to disease in which the mother or child could be in danger.

Tdap, influenza and hepatitis

As of 2013, two vaccines, IIV for influenza and Tdap for diphtheria, tetanus and pertussis, are recommended by the ACIP to be administered to all women of reproductive age before, during or after pregnancy (National Center for Immunization and Respiratory Diseases, 2011) (Table 1). Several other vaccines, including Hepatitis A and B and

Table I **Current CDC recommendations of maternal vaccination.**

Vaccine	Type/form	Before pregnancy	During pregnancy	After pregnancy
Hepatitis A	Inactivated	Yes, if indicated	Yes, if indicated	Yes, if indicated
Hepatitis B	Inactivated	Yes, if indicated	Yes, if indicated	Yes, if indicated
HPV	Inactivated	No (under study)	No (under study)	Yes, if indicated (to 26 years of age)
Influenza	Inactivated	Yes	Yes	Yes
	Live attenuated	Yes, if under 50 and healthy; avoid conception for 4 weeks	No	Yes, if under 50 and healthy; avoid conception for 4 weeks
MMR	Live attenuated	Yes, if indicated; avoid conception for 4 weeks	No	Yes, if indicated. To be given immediately post-partum if susceptible to rubella
Meningococcal	Polysaccharide	Yes, if indicated	Yes, if indicated	Yes, if indicated
	Conjugate	Yes, if indicated	Yes, if indicated	Yes, if indicated
Tdap	Toxoid Inactivated	Yes, if indicated	Yes, vaccinate during each pregnancy between 27–36 weeks of gestation	Yes, immediately post-partum if not given previously
Tetanus/diphtheria	Toxoid	Yes, if indicated	Yes, if indicated (Tdap preferred)	Yes, if indicated
Varicella	Live attenuated	Yes, if indicated; avoid conception for 4 weeks	No	Yes, give immediately post-partum if susceptible
Anthrax	Subunit	Yes, if indicated	No, unless risk of exposure is significant	No, unless risk of exposure is significant
BCG	Live attenuated	Yes, if indicated	No	No
Japanese Encephalitis	Inactivated	Yes, if indicated	Insufficient data for recommendation	Insufficient data for recommendation
MPSV4	Polysaccharide	Yes	No, unless risk of exposure is significant	No, unless risk of exposure is significant
Rabies	Inactivated	Yes, if indicated	No, unless post-exposure	No, unless post-exposure
Typhoid	Live attenuated	Yes, if indicated	Insufficient data for recommendation	Insufficient data for recommendation
Smallpox	Live attenuated	Yes, if indicated	No, unless post-exposure	No, unless post-exposure
Yellow fever	Live attenuated	Yes, if indicated	No, unless risk of exposure is significant	No, unless risk of exposure is significant

CDC, Centre for Disease Control and Prevention; HPV, human papillomavirus; MMR, Measles, mumps, rubella; BCG, baccilus (germ) of Calmette and Guerin; MPSV4, Meningococcal polysaccharide vaccine.

meningococcal, are recommended for women before, during or after pregnancy when risk factors exist (Centers for Disease Control and Prevention, 2013b).

Sub-optimal vaccine usage in the obstetric population

Despite the recommendations and advocacy by many public health organizations worldwide, the concept of maternal vaccination has not been widely accepted by the general public or become a priority among medical professionals. For example, even with the encouraging data from post-licensure studies on maternal Tdap and influenza vaccinations suggesting that the perinatal use of these vaccines is safe and could be key to closing the gap between maternal immunologic protection and traditional immunization schedules (discussed below), the maternal influenza vaccination rate has been estimated to be only ~50% in the USA (Centers for Disease Control and Prevention, 2013a). There are no retrospective studies on the rate of Tdap vaccination during pregnancy at the time of this review, and such information is even more sparse for other vaccines. Apart from the cultural, legal, educational and logistic barriers that are restricting the boarder usage of maternal vaccines, the lack of concrete scientific knowledge on the protective efficacy and adverse effects on the short- and long-term health status of various pregnant and pediatric populations, especially of the less studied vaccines, may have contributed to the underimmunization of pregnant women by medical professionals (Moffatt and McNally, 2013).

Concerns over maternal vaccination

Safety

Successful examples of maternal vaccines, such as influenza IIV, have shown efficacy in reducing maternal, fetal and neonatal morbidity due to infection or other pregnancy complications (Zaman *et al*., 2008; Omer *et al*., 2011; Steinhoff *et al*., 2012; Richards *et al*., 2013; El-Kady *et al*., 2014; Legge *et al*., 2014). Yet many concerns have been raised over maternal vaccination, which need to be addressed by further research. Apart from the ethical and legal issues (Riley and Minkoff, 2014), the potential short- and long-term deleterious effects of *in utero* exposure to maternal vaccines on the fetus and offspring are prominent concerns.

Prior to the recommended use on pregnant women, both IIV and Tdap vaccines were extensively studied in non-pregnant populations. However, the renewed ACIP recommendation of Tdap vaccination in every pregnancy, as mentioned earlier, has spurred increased interest in post-licensure studies to examine the effects that Tdap may have on pregnancy outcomes. It was recently reported that no negative consequences of administration to infants, regardless of the timing of vaccination in pregnancy, was found (Shakib *et al*., 2013), and maternal administration of Tdap correlated with a higher level of neonatal Pertussis-specific antibodies between birth and the first vaccine dose (Hardy-Fairbanks *et al*., 2013). In the case of influenza, the long-standing observation of its heightened severity on the mother and the fetus from across the world (Callaghan *et al*., 2010; Liu *et al*., 2011; Beigi, 2012; Hansen *et al*., 2012; Soydinc *et al*., 2012; Beau *et al*., 2014) and the dramatic disease morbidity and mortality in pregnant women during the 2009 H1N1 pandemic (Creanga *et al*., 2010) have underscored the importance of maternal vaccination and promoted the ACIP recommendation. Several wide-ranging surveillance studies in North America, Europe, Asia, Australia and Latin America all found no evidence to suggest that the IIV vaccine posed significant risk to either the mother or the fetus (Lim *et al*., 2010; Moro *et al*., 2011; Omon *et al*., 2011; Fell *et al*., 2012; Mackenzie *et al*., 2012; Oppermann *et al*., 2012; Pasternak *et al*., 2012; Carcione *et al*., 2013; Conlin *et al*., 2013; Irving *et al*., 2013; Louik *et al*., 2013; Nazareth *et al*., 2013; Nordin *et al*., 2013). In terms of hepatitis vaccination, there appears to be little or no data evaluating the effectiveness of the inactivated hepatitis vaccines in perinatal contexts. Centers for Disease Control and Prevention (CDC) guidelines recommend usage only if 'other high-risk conditions or indications are present' (National Center for Immunization and Respiratory Diseases, 2011). Examination of the Vaccine Adverse Event Reporting System (VAERS) over a 13-year period between 1996 and 2013 found no adverse events correlated with either hepatitis A or hepatitis B vaccines. In fact, several studies have pointed out that both hepatitis A (Moro *et al*., 2014) and hepatitis B (Ayoola and Johnson, 1987; Gupta and Ratho, 2003; Moro *et al*., 2014) vaccines are safe to administer, and also in the case of hepatitis B, that the vaccine clearly imparted high levels of immunogenicity to both the mother and fetus (Gupta and Ratho, 2003). Of note, the Hepatitis B vaccine series is recommended by the ACIP to be started on all neonates before hospital discharge.

For the other maternal vaccines routinely recommended in the CDC guidelines, there remains a significant gap in our knowledge of their short- and long-term safety. Studies on inadvertent pneumococcal polysaccharide, rubella or yellow fever vaccination cases found no significant maternal or fetal risk (Nasidi *et al*., 1993; Centers for Disease Control and Prevention, 1997; Castillo-Solorzano *et al*., 2011). However, follow-up requires both voluntary reporting and retrospective analysis involving significant speculation. Virtually nothing is known regarding a wide category of other vaccines that are considered 'non-routine', i.e. against possible biological agents, such as anthrax, or diseases which are exceedingly uncommon in the developed world, such as typhus or smallpox. In most cases, the available recommendations rely heavily on a theoretical benefit-to-risk ratio (Centers for Disease Control and Prevention, 2013b). Finally, questions continue to surface regarding the safety of vaccine components (i.e. thimerosal), long-term childhood neurodevelopmental conditions (i.e. autism) and venues to seek relief in the event of an identifiable vaccine-related injury. Despite reassurances from agencies, such as the Institute of Medicine (IOM), CDC and American Congress of Obstetricians and Gynecologists (ACOG), based on expanding reports of both short and long-term vaccine safety, the responsibility lies with the scientific community to continue a vigilant watch through basic research efforts and post-marketing surveillance systems (Poland, 2011).

Interference with infant response to vaccination

Another major concern surrounding maternal vaccination stems from the long-standing observation that the presence of maternal antibodies in the infant is able to interfere with the infant's humoral immune response to vaccines both systemically and at mucosal districts (Burstyn *et al*., 1983; Enriquez-Rincon and Klaus, 1984; Claesson *et al*., 1989; Daum *et al*., 1991; Booy *et al*., 1992; Sarvas *et al*., 1992; Yamazaki

et al., 1994; Englund et al., 1995; Troisi et al., 1997; Dagan et al., 2000; Kanra et al., 2000; Crowe et al., 2001; Getahun and Heyman, 2009), although cell-mediated immune responses are not affected (Martinez et al., 1997, 1999; Siegrist et al., 1998a, b). The inhibitory effect on infant response to vaccination has been, however, highly variable among different vaccines and even different studies of the same vaccine (Siegrist, 2003).

Many mechanisms of how maternal antibodies may inhibit infant humoral immune response to vaccines (Table II) can be postulated, some of which are based on the understanding of the immunosuppressive mechanism of passive intravenous immunoglobulins (IVIGs) (Schwab and Nimmerjahn, 2013). However, studies on how maternal antibodies may actually interfere with vaccine-induced humoral immunity in infants are needed, as maternal antibodies differ from IVIGs in quantity, structure, composition and function, such as half-life, glycosylation pattern, isotype and affinity for antigens and Fc receptors, and may interfere with the infant immune response via distinct mechanisms from those used by IVIGs. For example, the significant increase in the production of maternal asymmetric IgG with an extra carbohydrate moiety in one of the F(ab') domains during pregnancy (Gutierrez et al., 2005) may allow such IgG molecules to uniquely function as univalent blocking antibodies against vaccine antigens differently from IVIGs in infants (Pasetti et al., 1997). Since maternal antibodies decline in the infant, interference of the infant humoral immunity to vaccination was found to mainly impact primary immunization in early infancy but not subsequent boosting (Glezen, 2003). However, this should not be a reason to dismiss maternal immunization, as a reduced antibody titer after infant vaccination may be acceptable if the high morbidity and mortality can be mitigated in the first months of life by maternal vaccination. Indeed, studies in mice show that maternal antibodies can promote immune maturation in the offspring (Malanchere et al., 1997; Fink et al., 2008). The pros and cons of maternal vaccination on the immune responses to any given infant vaccination protocol should therefore be evaluated individually.

Humoral immune modulations in pregnancy that influence vaccine efficacy and safety

All of the current maternal vaccination formulations are initially designed for and tested in the non-pregnant population. However, substantial immune modulations take place both systemically and in the reproductive mucosa during different stages of pregnancy, highlighting the distinct possibility of sub-optimal or qualitatively different vaccine responses in pregnant women. Research is thus needed to elucidate pregnancy-associated immune alterations in both normal and complicated pregnancies that can influence vaccine responses. The various pregnancy-associated changes in the T, natural killer, myeloid, cytokine and chemokine compartments have been discussed in several excellent reviews (Moffett and Loke, 2006; Mor and Cardenas, 2010, Chen et al., 2012; Pazos et al., 2012a; Erlebacher, 2013). As B cells are the final effectors of humoral immunity, we focus on the modulations in the B cell compartment and their potential influence on vaccine-induced antibody response.

The central and peripheral B cell compartments undergo quantitative changes during pregnancy, with a contraction of peripheral B cell numbers (Fig. 2). Initial studies in mice showed a profound reduction of B cell precursors in the bone marrow from early pregnancy, which was likely mediated by estrogen (Medina et al., 1993, 2000). Consistently, the overall antibody titers to influenza infection are lower in pregnant mice (Medina and Kincade, 1994; Smithson et al., 1998; Chan et al., 2010). Similar changes have also been found in humans by many studies (Christiansen et al., 1976; Moore et al., 1983; Valdimarsson et al., 1983; Iwatani et al., 1988; Watanabe et al., 1997; Mahmoud et al., 2001a). Of note, steroid hormones regulate humoral immunity at multiple stages of B cell development. For example, the very early precursors of pro-B cells are particularly sensitive to negative regulation by

Table II Postulated mechanisms of maternal antibody-mediated inhibition of infant humoral immune response to vaccination.

Mechanism		Supporting references
$F(ab')_2$-dependent	Clearance of vaccine antigens by maternal IgG via opsonization and subsequent FcγR-mediated phagocytosis	Getahun and Heyman (2009)
	Neutralization of live viral vaccine epitopes by maternal IgG	Albrecht et al. (1977) and Naniche (2009)
	Inhibition of infant B cell recognition of vaccine epitopes by maternal IgG via antigenic masking	Wiersma et al. (1989), Jelonek et al. (1996), Nohynek et al. (1999) and Getahun and Heyman (2009)
Fc-dependent	Clearance of vaccine antigens by maternal IgG via FcγR-mediated phagocytosis after antigen opsonization	Getahun and Heyman (2009)
	Inhibition of infant B cell activation, survival and antibody production by maternal IgG via the inhibitory receptor FcγRIIB	Victor et al. (2010) and Kim et al. (2011)
	Inhibition of infant antigen-presenting cells by maternal IgG via the inhibitory receptor Dendritic Cell-Specific Intercellular Adhesion Molecule-3-Grabbing Non-integrin (DC-SIGN), also called CD209	Anthony et al. (2008)
	Saturation of infant endothelial or myeloid FcRn by maternal IgG and acceleration of catabolism of vaccine-induced infant IgG	Vieira and Rajewsky (1988), Junghans and Anderson (1996), Hansen and Balthasar (2002) and Li et al. (2005)
	Inhibition of infant dendritic cells (DCs) by ingested and absorbed maternal IgA via FcαRI	Pasquier et al. (2005) and Kanamaru et al. (2008)
	Inhibition of infant B cells and follicular DCs and macrophages by ingested and absorbed maternal IgA via Fcα/μR	Honda et al. (2009)

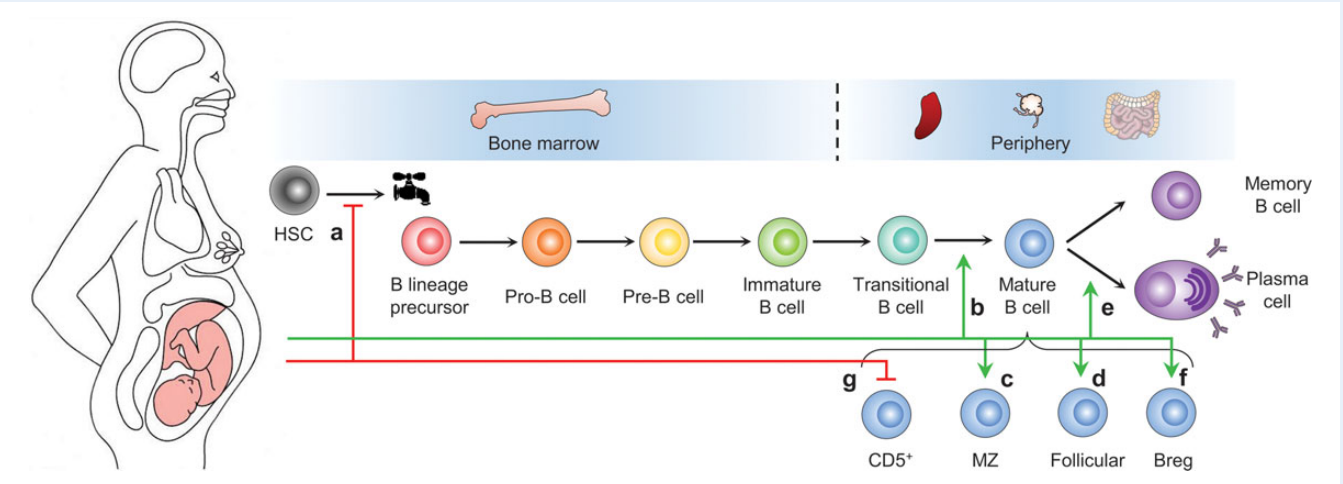

Figure 2 Pregnancy-associated humoral immune alterations that can influence vaccine responses. Pregnancy is accompanied by a marked suppression of the generation of B lineage precursors from hematopoietic stem cells (HSCs) in the bone marrow (a), leading to a reduction of the size of the B cell pool. This suppression of B lymphopoiesis is likely mediated by steroid hormones, such as estrogen. However, estrogen has an opposite effect at later stages of B cell differentiation by promoting the maturation of immature B cells (b) and the generation of marginal zone (MZ) B cells (c) and follicular B cells (d). The combined effect is a reduction of the percentages of immature and transitional B cells in the reduced B cell pool. Estrogen has also been shown to promote the development of plasma cells (e), whereas estrogen and human chorionic gonadotrophin (hCG) have been shown to promote the development of regulatory B cells (B_{regs}) (f). In normal pregnancy, peripheral $CD5^+$ B cells, which have been implicated in adverse pregnancy outcomes, are suppressed by a mechanism that is not well-known (g). This mechanism and the proper negative selection of autoreactive B cells in the bone marrow are critical to avoid the stimulation of potentially pathogenic B cells by estrogen during pregnancy. Of note, the identity of human B-1 cells is under contentious debate, and the developmental relationship between human B_{regs}, MZ B cells and B-1 cells is unclear.

estrogen (Kincade *et al.*, 2000; Medina *et al.*, 2001), allowing estrogen to control the size of the B cell pool, while estrogen has an opposite effect at later stages of B cell development, where it promotes B cell maturation and antibody production (Verthelyi and Ahmed, 1998; Grimaldi *et al.*, 2002, 2006). Consequently, normal or even elevated percentages of peripheral mature B cells are found during pregnancy in mice (Medina *et al.*, 1993). Estrogen has also been shown to be able to expand MZ B cells and follicular B cells in mice (Grimaldi *et al.*, 2001, 2006).

Coupled with such stage-specific regulation of B cells by estrogen, are the mechanisms that remove or reduce potentially pathogenic B cells during normal pregnancy. The percentage of circulating $CD5^+$ B cells (Bhat *et al.*, 1995), a population enriched with autoreactivity and partially overlapping with the human B-1 cells (Griffin *et al.*, 2011) recently postulated to be implicated in adverse pregnancy outcomes, such as recurrent pregnancy loss, pre-eclampsia and preterm birth (Kwak *et al.*, 1995; Beer *et al.*, 1996; Roberts *et al.*, 1996; Mahmoud *et al.*, 2001b; Tamiolakis *et al.*, 2001; Darmochwal-Kolarz *et al.*, 2002; Jensen *et al.*, 2012; Wang *et al.*, 2013), is reduced in healthy human pregnancy. Paternal antigen-specific maternal B cells are also suppressed (Ait-Azzouzene *et al.*, 1998, 2001). In addition, estrogen can induce regulatory B cells (B_{regs}) that express interleukin-10 and programmed death ligand-1 (Bodhankar *et al.*, 2011), which have been implicated with protective functions in pregnancy (Rolle *et al.*, 2013; Wang *et al.*, 2013). The mechanisms to remove or reduce auto- and allo-reactive B cells are critical, because if they fail, estrogen would stimulate the production of pathogenic antibodies by these B cells. Together with the predominant autoantibody production by human early immature B cells (Wardemann *et al.*, 2003), mouse and human data suggest a selective down-regulation of pathogenic B cells in normal pregnancy. This notion has important implications for the development of maternal vaccines, which should leverage the antibody-promoting function of steroid hormones, such as estrogen, and at the same time target the B cell populations in pregnant women to generate high levels of class-switched IgG while avoiding triggering B cells that can mount detrimental autoimmune or alloimmune reactions. This entails a thorough understanding of the type of B cells in pregnancy that are responsible for the production of protective antibodies in response to maternal vaccines, as well as the previous or current autoimmune diagnosis of the pregnant women to be vaccinated. The answer to this question is also relevant to the efficiency of placental antibody transfer to and persistence in the fetus, as different B cell populations can undergo class switching in response to different antigens, preferentially to specific IgG subclasses that vary in their binding affinities to FcRn (Costa-Carvalho *et al.*, 1996) and *in vivo* half-life (Morell *et al.*, 1970; Stapleton *et al.*, 2011). The analysis of safe and effective examples of maternal vaccines, including Tdap and IIV, in terms of the maternal B cell populations targeted and the composition of maternal antibodies produced, will offer clues to the answer of the above question.

Animal models for maternal vaccination

General guidelines

Epidemiological studies of pregnant women exposed to vaccines have proved to be a useful source of information for the efficacy and safety of these vaccines, but animal models are required to dissect the mechanism of vaccine-induced protection, side effects and to develop new

maternal vaccines. Historically, the development and testing of maternal vaccines has critically relied on animal models, which have served at least two purposes. They are used to understand the *in vivo* mechanism of pathogenesis and the protective immunity required to control and eradicate the pathogen. Once a lead vaccine candidate is identified, animal models are used to evaluate its safety, immunogenicity, pharmacokinetics and efficacy. Many species, including mouse (Oda *et al*., 1983; Paoletti *et al*., 2000; Abram *et al*., 2003; Chan *et al*., 2010; Rahman *et al*., 2010; Monney *et al*., 2012; Pazos *et al*., 2012a, b), rat (Heiman and Weisman, 1989, 1990; Zenner *et al*., 1993; Hernando-Insua *et al*., 2010; Kim *et al*., 2011), hamster (Freyre *et al*., 2012), guinea pig (Harrison *et al*., 1995; Bourne *et al*., 2001; Schleiss *et al*., 2007, 2013, 2014; Leviton *et al*., 2013), rabbit (Wessels *et al*., 1990, 1993; Barrow, 2012; Barrow and Allais, 2013), sheep (Perez-Sancho *et al*., 2014), pig (Elahi *et al*., 2006) and non-human primates (Paoletti *et al*., 2000; Barry *et al*., 2006; Warfel *et al*., 2014), have been used.

In addition to cost and the availability of reagents, various experimental species differ from humans in immune regulation, susceptibility to the pathogen, pathogenesis of infection, length of gestation, placenta physiology and the relative contribution of placental (or yolk sac) antibody transfer versus post-natal transfer of milk antibodies via milk (Table III). Certain species, such as ruminants, horses and pigs, have no or little placental transfer of maternal antibodies to the fetus (Tizzard, 1987), and intestinal absorption occurs for only the first 1–2 days after birth (Tizzard, 1987; Yoshida *et al*., 2004, 2006; Zaman *et al*., 2008), which makes these species unsuitable for testing the function of maternal vaccination in fetal or neonatal immune protection.

The World Health Organization has recommended general guidelines to assess the potential adverse effects of *in utero* exposure to maternal vaccines using animal models (World Health Organization, 2003). The animal is usually exposed to the vaccine from implantation to the completion of pregnancy via a route similar to that used clinically. For the species with a relative short gestation period, when compared with the time required to develop a vaccine response, vaccination before mating is necessary to allow the fetus to be exposed to full vaccine-induced response. The maximal human dose is recommended for the animal as a starting point. However, if toxicity is observed or if the large administration volume in not feasible for a smaller animal, a mg/kg dose that is higher than the human dose and immunogenic in the animal should be used. The titers of vaccine-induced antibodies in maternal, cord and fetal blood should be determined to verify fetal exposure. Multiple doses may be required depending on the nature of the vaccine formulation and response. Booster immunizations during pregnancy may be necessary to maintain high antibody titers throughout the gestation period so that the embryo is exposed to both the maximal maternal immune response and the complete components of the vaccine formulation. Fetal viability, resorption, abortion, weight and morphology should be determined. In addition, pups should be monitored until weaning for growth, weight gain and viability, whereas the mother should be monitored for nursing activity.

The lesson from mice

Mice have been extensively used for maternal vaccination studies, including influenza (Chan *et al*., 2010; Pazos *et al*., 2012a, b), pertussis (Oda *et al*., 1983; Quinello *et al*., 2010) and GBS (Lagergard *et al*., 1990; Wessels *et al*., 1990, 1993; Madoff *et al*., 1992; Paoletti *et al*., 2000). In the case of influenza, the effect of infection on maternal immunity and pregnancy outcome are largely conserved. Infection results in more severe morbidity and mortality in pregnant mice and adversely impacts litter size and health (Siem *et al*., 1960; Mackenzie *et al*., 1977; Williams and Mackenzie, 1977; Chan *et al*., 2010). Pregnant mice also have altered or delayed cytokine production similar to that in pregnant women (Chan *et al*., 2010), which was likely mediated by estrogen (Pazos *et al*., 2012b). For pertussis, placental and post-natal transfer of maternal antibodies confers neonatal protection similarly to that in humans, although substantially greater protection has been found to be transferred via milk post-natally (Oda *et al*., 1983; Quinello *et al*., 2010). For GBS, the murine model of maternal vaccination followed by neonatal challenge has been used to study both maternal immunogenicity and the efficacy

Table III Comparison of human and the common animal models for maternal vaccination research.

Features	Human	Mouse	Rat	Guinea pig	Rabbit	Rhesus monkey	Pig
Gestational length	270–280 days	20 days	22 days	59–72 days	32 days	164 days	115 days
Placenta morphology	Hemochorial, discoid, villi	Hemochorial, discoid, labyrinth	Hemochorial, discoid, labyrinth	Hemochorial, discoid, labyrinth	Hemochorial, discoid, labyrinth	Hemochorial, bidiscoid, villi	Epitheliochorial, diffuse, folded
Source of progesterone	Corpus luteum, then placenta and fetal membrane	Corpus luteum	Corpus luteum	Corpus luteum	Corpus luteum	Corpus luteum, then placenta	Corpus luteum
Progesterone withdrawal in parturition	No*	Yes	Yes	No*	Yes	No*	Yes
Prenatal transfer of IgG	Placenta, FcRn	Inverted yolk sac, FcRn	Inverted yolk sac, FcRn	Inverted yolk sac, fetal gut, FcRn	Inverted yolk sac, FcRn	Placenta, FcRn	No transfer
Post-natal transfer of IgG	Gut (1–2 days after birth), FcRn	Proximal small intestine, FcRn	Proximal small intestine, FcRn	No significant transfer	No significant transfer	Gut (1–2 days after birth), FcRn	Gut (2–3 days after birth), FcRn

*Functional progesterone withdrawal may occur via the expression of inhibitory progesterone receptors in parturition.

of neonatal protection (Madoff *et al.*, 1992; Rodewald *et al.*, 1992; Paoletti *et al.*, 1994). Preclinical evaluation of maternal GBS glycoconjugate vaccines has largely relied on mouse models. Female mice are vaccinated before pregnancy and their offspring are challenged with viable GBS (Madoff *et al.*, 1994; Paoletti *et al.*, 1994). An immunogenic GBS glycoconjugate vaccine, but not capsular polysaccharides, has been shown to confer protection of most of the pups. Mice have also been used to test the therapeutic efficacy of GBS glycoconjugate vaccine-induced passive immunity in human antisera (Paoletti *et al.*, 1997).

Nonetheless, mice differ from us in many key features pertaining to pregnancy, including gestational length, placentation and endocrinology (Table III), as well as a myriad of other differences in the immune system (Mestas and Hughes, 2004). Various strains of mice also exhibit subtle or even substantial differences in the susceptibility to certain pathogens (Johnson, 2012), which, conceivably, reflects the intrinsic differences in their immune systems. Therefore, the use of mouse models to research maternal vaccination is not expected to completely replicate human physiology, but should be coupled with human studies in an iterative manner, whereby hypotheses drawn based on the observations in humans are tested in mouse models under controlled conditions with detailed sample and data collection, which in turn refines the hypotheses to be further validated in additional human studies (Bonney, 2013). Only by adopting such an iterative approach that mirrors the cycle of vaccine development (Trautmann and Sekaly, 2011) can animal and human studies synergize to make existing maternal vaccines more effective and safer and to facilitate the development of new vaccines.

Conclusions and future directions

Maternal vaccination has emerged as a promising public health approach to prevent or combat maternal and neonatal morbidity. Considerable achievements have been made in the past decade, with a number of vaccines being universally recommended for pregnancy. However, the public acceptance of maternal vaccination has been low in many countries. Besides the ethical, legal and socioeconomic restraints, significant gaps exist in our knowledge of the efficacy and safety of maternal vaccines in pregnant women and those susceptible to high-risk pregnancies, and no maternal vaccines against a large number of old and emerging pathogens are available. To tackle these scientific challenges and provide the public with informed choices in vaccination, obstetricians, gynecologists, reproductive biologists and immunologists must transcend the traditional disciplinary barriers and work in concert, to be guided by a mechanistic understanding of the maternal, fetal and neonatal immunologic responses to vaccines. Our shallow overview of the various topics in this review is precisely intended for such a purpose.

Can we be faster and more effective?

The empirical quest of maternal vaccines has largely relied on a reductionist approach of hypothesis creation followed by experimental validation in animal models and clinical trials. This approach can be time consuming, not allowing the rapid development of new vaccines, especially in case of an emerging pandemic. Neither does it offer a systemic view of the complex behavior of the maternal immune system after vaccination. Recently studies have highlighted the power of reverse vaccinology for systematic and improved antigen discovery (Sette and Rappuoli, 2010) and systems vaccinology to profile vaccine response (Pulendran *et al.*, 2010) and even to predict vaccine efficacy (Querec *et al.*, 2009; Nakaya *et al.*, 2011; Li *et al.*, 2014). We believe the application of such approaches at all stages of maternal vaccination research, from animal experimentation to human trials and evaluation, will dramatically improve the speed, accuracy and safety of maternal vaccine targeting. Lastly, as the efficacy of maternal vaccines also significantly relies on the secretion of antibodies at the maternal–fetal interface and in the mammary gland, a thorough understanding of the unique mechanisms of mucosal immune regulation and the microbiota influence (Brandtzaeg, 2010, Chen and Cerutti, 2010b) as well as the incorporation of mucosal immune assessment into maternal vaccine experimentation and evaluation protocols are required.

Acknowledgements

We apologize to those authors whose work we could not cite due to space limitations.

Authors' roles

A.N.F. and B.L.U. reviewed the literature and wrote the manuscript; B.G. revised the manuscript; K.C. conceived the study, reviewed the literature, and wrote and revised the manuscript.

Funding

The authors' research is supported by the US National Institutes of Health (U01 AI95776 Young Investigator Award), American Congress of Obstetricians and Gynecologists (Merck Industrial Research Award), Burroughs Wellcome Fund (Preterm Birth Research Award), Wayne State University Perinatal Initiative (176512), Wayne State University Office of the Vice President for Research and Barbara Ann Karmanos Cancer Institute to K.C.

Conflict of interest

None declared.

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