Maternal Immunization: Opportunities for Scientific Advancement

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Maternal immunization is an effective strategy to prevent and/or minimize the severity of infectious diseases in pregnant women and their infants. Based on the success of vaccination programs to prevent maternal and neonatal tetanus, maternal immunization has been well received in the United States and globally as a promising strategy for the prevention of other vaccine-preventable diseases that threaten pregnant women and infants, such as influenza and pertussis. Given the promise for reducing the burden of infectious conditions of perinatal significance through the development of vaccines against relevant pathogens, the Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH) sponsored a series of meetings to foster progress toward clinical development of vaccines for use in pregnancy. A multidisciplinary group of stakeholders convened at the NIH in December 2013 to identify potential barriers and opportunities for scientific advancement in maternal immunization.

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Maternal immunization is an effective and increasingly attractive strategy for the prevention of infectious diseases in both mothers and their infants. Maternally derived pathogen-specific antibodies induced by vaccination during pregnancy can provide infants with the protection they need during a period of vulnerability. A particularly important example is the substantial decline in neonatal tetanus globally as a result of the Maternal and Neonatal Tetanus Elimination program in conjunction with the World Health Organization (WHO). Widespread administration of tetanus toxoid vaccine to pregnant women, in combination with attention to improved perinatal hygienic practices and vaccination of all women of childbearing age, has produced a substantial decrease in total attributable neonatal deaths, from 14% to 5%, over a 20-year time period (1990–2010) in countries implementing this initiative [1]. More recently, influenza and pertussis vaccination has also been recommended for all pregnant women [2–5].

Support from numerous advisory committees and professional societies (eg, Advisory Committee on Immunization Practices [ACIP], American College of Obstetricians and Gynecologists, American Academy of Family Physicians, American Academy of Pediatrics, National Vaccine Advisory Committee) has contributed to increased uptake of vaccines during pregnancy in the United States. Estimated influenza vaccine coverage during pregnancy has increased from approximately 15% in 2008 to approximately 45%–50% during the
2013–2014 influenza season [6, 7]. Limited data suggest gains, albeit more modest, in antenatal vaccine pertussis receipt, starting from approximately 3% at baseline (prior to the updated recommendation for all pregnant women to receive a dose each pregnancy) to an estimated 6%–21% [8, 9]. Efforts must continue to sustain and improve upon these successes.

Influenza vaccine is the most frequently administered vaccine during pregnancy in the United States. Although influenza vaccine has been recommended for pregnant women for >50 years, the uptake has been relatively slow until very recently, when coverage increased after the 2009 influenza A(H1N1) pandemic [6,7,10]. Despite this relatively slow uptake, the ongoing administration of influenza vaccine to pregnant women for decades has produced a substantial amount of reassuring observational safety data. No studies have shown harmful consequences of inactivated influenza vaccine in pregnancy, and the overwhelming preponderance of data demonstrates safety in both mothers and their children [11–15]. However, the majority of available safety and effectiveness information comes from studies that are not randomized clinical trials (RCTs). This is largely due to noninclusion of pregnant women in prelicensure investigations as a specific licensure indication for administration of influenza vaccine to pregnant women was never sought. Most currently available data on the safety and effectiveness of influenza immunization during pregnancy originates from retrospective population-based cohort studies and database reviews. The available RCTs are small in size, with limited statistical power [15–17].

Even fewer data are available on other vaccines used in pregnancy. Many of these vaccines are given to pregnant women under special circumstances—for example, medical comorbidities (pneumococcal vaccine), travel to endemic areas (meningococcal vaccine), or occupational exposures (hepatitis B). Inactivated vaccines approved for nonpregnant populations are frequently recommended for pregnant women when the risk of the disease they prevent outweighs any theoretical potential risk of the vaccine. Because the vaccines recommended during pregnancy do not contain live replicating organisms (ie, are not live attenuated), most practitioners are typically comfortable with this practice. With this background, the benefits achievable from robust investigation of the safety and effectiveness of recommended and new candidate vaccines designed specifically for use in pregnancy assume a high priority [18–20].

Identifying opportunities for and barriers to advancement in the field of maternal immunization is a large endeavor. Many of the opportunities and barriers are generalizable to all maternal immunizations, whereas others are very specific to the pathogen and its disease course. For example, our understanding of maternal–fetal physiology and immunology as it relates to vaccine challenge continues to evolve. Responses of the infant immune system to in utero exposures to both pathogens and maternally derived antibodies have received some attention and would benefit from additional study [21–23]. Additional areas for needed inquiry include determining the best gestational timing for each vaccination, the levels of antibody and the correlates of protection derived from breast milk, and infant responses to active immunization in the presence of elevated transplacentally derived maternal antibody after vaccination. Finally, clinical trials in pregnant women pose unique challenges best addressed by considering lessons learned from the use of already recommended vaccines and regulatory needs supporting licensure of new vaccines to be administered in pregnancy.

In an ongoing effort to foster progress by supporting and promoting the scientific development of maternal immunization and provide guidance on the development and utilization of vaccines in pregnant women, the Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) has convened a series of ongoing meetings of experts in infectious diseases, vaccinology, maternal fetal medicine, pediatrics, neonatology, epidemiology, clinical research, pharmacology, and clinical trial design from government agencies, academia, and industry over the past few years. Previous guidance from earlier meetings have been already reported [24, 25]. The overall goals of the current meeting that took place in December 2013 (and are addressed in this report) were to identify potential opportunities for scientific advancement in maternal immunization as well as the recognition of potential barriers to such advancement. Motivating these efforts was the recognition that (1) there is large potential for maternal immunization in the prevention of disease in mothers and infants as a global public health strategy; (2) maternal immunization is currently an underutilized strategy; (3) more comprehensive data addressing maternal and infant vaccine safety, immune responses in the mother and infant, and the effect of vaccines on disease burden are needed; and (4) performing clinical trials in pregnant women poses unique challenges. Broad areas recognized as key opportunities for knowledge acquisition and advancement in the field of maternal immunization are listed in Table 1.

Pathogen Epidemiology and Maternal–Fetal Physiology
For the majority of pathogens, country-specific burden of disease data among pregnant women and their infants are relatively limited [26–30]. Likewise, the presence and/or relevance of pathogen colonization and the interface with clinical infection is often not well understood. For some pathogens, such as group B Streptococcus (GBS), there are geographic-specific subtype distribution data; however, for large sections of the developing world, no such data on GBS burden exist [31]. Improved knowledge of pathogen-specific disease epidemiology before and after implementation of a maternal immunization program would allow documentation of objective program-specific benefits.
A successful model of such a comprehensive surveillance program is the Active Bacterial Core surveillance network sponsored by the Centers for Disease Control and Prevention (CDC), which provides surveillance data on Haemophilus influenzae, Neisseria meningitidis, group A Streptococcus, GBS, Streptococcus pneumoniae, and methicillin-resistant Staphylococcus aureus in multiple large diverse US populations [32]. While recognizing the many challenges to establishment of a comprehensive surveillance program (eg, large costs, infrastructure availability), having these data would allow determination of background rates of colonization and disease prevalence, as well as underlying rates of maternal and infant morbidity and mortality. Such investigations would require support from multiple sources, including access to hospital and laboratory data to assess the burden of disease, support from the public health community to make data acquisition a priority, and substantial financial support from governmental and/or nongovernmental funding agencies.

Importantly, in 2011 NIH (NIAID/Eunice Kennedy Shriver National Institute of Child Health and Human Development) announced a new funding opportunity (“Strategies for the Protection of Pregnant Women and Infants Against Infectious Diseases [R01]”) to encourage new and innovative mechanistic studies of pathogens that impact placental function and fetal well-being. The goal was to inform development of interventions to reduce the burden of infection-related pregnancy loss and infant morbidity and mortality [33]. Focused opportunities resulting from this funding included the evaluation of (1) pathogen-mediated placental pathology and/or dysfunction, (2) transplacental transmission of pathogens and their components, and (3) pathogen-mediated pregnancy loss and preterm delivery. It is hoped that information learned from studies in response to this funding announcement will produce a broader understanding and augment further progress in the field.

An additional area in which to gain further knowledge is the specifics of maternal antibody transfer across the placenta. Currently the NIH has highlighted a new focus on the placenta as a vitally important organ for improved understanding that may provide opportunities for delineation of such information [34]. Additional information regarding the antibody transfer rate, the windows of risk for disease and infectivity, and the rate of antibody decay in the fetus and infant would greatly augment the field. Importantly, the duration of the immune response, the need for repeat vaccination or boosting, and the production and regulation of B- and T-cell responses in mothers and infants, as well as potential biomarkers for these endpoints, are all areas under investigation [35–38]. Although some preliminary and pathogen-specific data exist for measles and polio, mechanisms underlying breast milk antibody production following vaccination and effects on the infant or the protection such antibodies generate after enteral passage to the infant are also an area of scientific opportunity [39, 40]. The critically important effect of passively acquired maternal antibodies on the infant’s immune response to active immunization and/or to natural infection would also benefit from additional investigation [41–45]. With promising data and clinical experience from maternal immunization programs for influenza, tetanus, and now pertussis, some of the above-mentioned questions (and others) can be investigated further to aid in our understanding of the dynamics of vaccines currently administered during pregnancy and potential future vaccines such as GBS and respiratory syncytial virus (RSV) [18, 19].

**Monitoring Vaccine Safety Following Maternal Immunization**

Studying a medication or vaccine given during pregnancy is confounded by the risk of pregnancy-related events that occur independently from the medication or vaccine but might impact the obstetric outcome. As discussed by Munoz et al, baseline rates of pregnancy and obstetric-related events in all settings must be accounted for when examining the safety of any intervention in pregnancy [24]. Common concerns with any investigational product administered during pregnancy relate to risk of congenital anomalies and the potential for adverse pregnancy outcomes. However, the likelihood of congenital anomalies and/or adverse pregnancy outcomes from receipt of inactivated vaccines is extremely unlikely, given the lack of biological plausibility for such occurrences and because these are typically administered outside the period of embryogenesis (ie, the first 13 weeks of gestation) [46]. Additionally, vaccines administered inadvertently in the first trimester of pregnancy have not resulted in increased rates of congenital anomalies.
above the background rates [2]. Nevertheless, for investigational vaccines, this risk of congenital anomalies remains a critical question and must be carefully considered when designing studies in pregnant women.

The long-term effects among women and infants years after maternal immunization have not been fully characterized. The potential contribution of vaccines to rare adverse events in infants with certain chronic conditions of unknown etiology is also an important area for study. Various working groups continue to utilize expert panel and reporting databases to detect and continue to evaluate various clinical scenarios and their association (or lack thereof) with vaccination. Some of these systems include Vaccine Adverse Event Reporting System, Vaccines and Medications in Pregnancy Surveillance System, and Vaccine Safety Datalink. Additionally, other groups such as the Brighton Collaboration and the CDC’s Clinical Immunization Safety Assessment Project, as well as the WHO’s Global Advisory Committee on Vaccine Safety, are expanding their investigations into the safety of vaccines administered during pregnancy. These combined systems could provide much-needed data on current vaccines being used during pregnancy. The optimal system for establishing and monitoring vaccine safety during pregnancy has not yet been fully established. Increased efforts to coalesce the available data from the noted vaccine surveillance systems for the currently used vaccines along with prelicensure safety data obtained by enrolling pregnant women in newer maternal vaccine trials will greatly augment the field.

**Regulatory Considerations**

From a regulatory perspective, opportunities exist to advance the field of maternal immunization for both candidate vaccines in development and already licensed vaccine products.

Early infancy is a precarious period of life, in part because of the high attack rate of several infectious diseases. For some of these infectious agents (eg, GBS, RSV), no licensed vaccine products are available. Utilization of maternal immunization platforms to demonstrate prevention of these diseases in infants through maternally transferred antibody is a promising approach for novel vaccine candidate development [18–20].

For licensed vaccines (eg, tetanus, diphtheria, and acellular pertussis [Tdap] and influenza vaccines), opportunities for advancement from a regulatory perspective exist primarily in 2 categories: clinical development of additional indication(s) for use specifically during pregnancy and further characterization of the safety profile in postmarketing surveillance.

ACIP’s recommendations for use of Tdap and influenza vaccines during pregnancy have resulted in increasing rates of maternal immunization [3, 6–10]. (This does not represent “off-label” use, because the relevant vaccines are not contraindicated in pregnancy and can be given to a pregnant woman “if clearly needed.”) However, licensure of a separate, specific indication for use during pregnancy would give practitioners additional data and guidance in the package insert to support such use. This would likely increase both provider and patient awareness, leading to further uptake. Several randomized, blinded, controlled studies of licensed vaccines in pregnancy have been, and are being, conducted by nongovernmental organizations and other groups [18–20, 45, 47, 48]. Licensed vaccine manufacturers might consider partnering with these groups and working with the US Food and Drug Administration (FDA) Office of Vaccines Research and Review to delineate a package of data sufficient to support licensure of a new indication for use specifically in pregnancy.

With regard to postmarketing safety surveillance, these efforts have consisted primarily of passive surveillance and pregnancy registries. The FDA recently convened a public meeting to assess the performance of various approaches to postmarketing safety surveillance for drugs and biologics [49]. At this meeting, the many limitations of pregnancy registries for vaccine products (ie, high loss to follow-up, lack of denominator, lack of internal control) were noted. Manufacturers and other stakeholders could also consider alternatives to further characterization of safety postmarketing, such as studies in large claims databases.

**Implementation of a Maternal Immunization Program**

Challenges and potential barriers to improved vaccination uptake during pregnancy relate to both providers and patients. For obstetric providers, recommending the vaccine is a critical intervention that is a demonstrated powerful driver of vaccine acceptance [7]. The ability of obstetric providers to become and remain strong advocates for maternal immunization may be hampered by insufficient experience with vaccinations during training or to the logistical challenges of vaccine administration in their clinical practice [50, 51]. Reimbursement inconsistencies, liability concerns, and comprehension of available safety data as well as compliance with safety reporting requirements and vaccine tracking represent separate challenges to the obstetric provider’s role as a vaccinator [7]. Provider awareness or acceptance of the role as a vaccinator has an enormous effect on vaccine acceptance. Additionally, increased data and experience surrounding the benefits of maternal immunization can also have a powerful effect going forward. Considering the patient perspective, there is unlimited exposure to media outlets, publications, and forums with differing messages on vaccination. Obstetric providers should give guidance on credible sources of vaccine information. Education on vaccine implementation and practices as well as information about adverse events should be provided during obstetrics residency training and to practitioners through continuing medical education. Expanded educational efforts can help counter negative messages and ultimately lead to more standardized approaches and
Successful antenatal vaccination programs. Future regulatory approval for pregnancy indications of newer vaccines under development would likely augment provider vaccine recommendation efforts, driving acceptance.

**Vaccine Education for Providers and Patients**

Maternal immunization offers many opportunities for education to providers and patients about the protection of the mother and infant with one intervention. Despite being immunotolerant to their fetus, pregnant women generally have immune responses to vaccines similar to those of nonpregnant adults [11, 35, 52, 53]. Furthermore, vaccination during pregnancy allows adequate time for education, planning, administration, and follow-up because women are accessible to obstetric care providers during the length of their antepartum and postpartum care. Effective vaccination against potential perinatal pathogens could potentially decrease use of antimicrobials in mothers and infants and curb potential infant comorbidities from invasive infection.

Maternal immunizations are also an investment in better health outcomes for both pregnant women and their infants. The potential benefits gained following successful implementation of vaccination programs have historically shown a significant return on investment in both direct and societal costs, as well as the documentable benefits of a healthy and happy life [54]. Investments in implementation research and provider education should focus on vaccine training, recommended vaccine use, and adverse event reporting, as well as safety, acceptance, and benefits of vaccines in pregnant women. Interventions to educate the public and providers on the safety and benefits of the vaccine, targeting misconceptions regarding vaccine safety and benefits, may serve to improve vaccine uptake.

Delayed successes in maternal immunization programs are partially due to a lack of compliance among obstetric providers with current recommendations. Successful implementation of current and future maternal immunization guidelines will require improved awareness among obstetric providers and patient education about the health benefits for themselves and their infants. Maintaining close collaboration between international professional organizations, physicians, scientists, and regulatory authorities will help enable greater uptake of recommended vaccines in pregnant women.

**CONCLUSIONS**

Maternal immunization is a rapidly developing field with tremendous potential to realize large-scale benefits for both maternal and infant health. Numerous instrumental opportunities were identified to help realize this potential. Recognizing these areas also serves to highlight the large volume of work that is needed in this field. These areas broadly include improved understanding of relevant pathogen-specific epidemiology, maternal and infant response to immunization, breast milk antibody generation after immunization and effects on the infant, regulatory climates fostering research and development of new vaccines for pregnant women, investigations of vaccine safety and efficacy, and improved understanding of effective strategies to implement current and future maternal immunizations. The delineation of these and other relevant issues will undoubtedly translate into lower maternal and infant infectious morbidity in the future. Doing so will also help the scientific and public health community fulfill the promise of maternal immunization for future generations.

**Notes**

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