Maternal immunization efforts of the National Institutes of Health

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ABSTRACT

Over the last 35 years, efforts at the National Institutes of Health (NIH) to protect mothers and their infants against infectious diseases have involved a bench-to-bedside approach. Basic and translational research that provided a foundation for clinical trials of vaccines in pregnancy include natural history and vaccine antigen identification studies. Development of laboratory assays and reagents have been funded by NIAID; these are critical for the advancement of vaccine candidates through the preclinical and clinical steps along the maternal immunization research pathway to support vaccine efficacy. Animal models of maternal immunization have been developed to evaluate efficacy of vaccine candidates. Clinical studies required development of maternal immunization protocols to address specific pregnancy related issues, for enrollment and safety assessment of mothers and their infants. NIH has organized and participated in meetings, workshops and other collaborative efforts with partners have advanced maternal immunization efforts. Partners have included many institutes and offices at NIH as well as other Department of Health and Human Services agencies and offices (Food and Drug Administration, Centers for Disease Control and Prevention, National Vaccine Program Office), World Health Organization, academic investigators, Biotech and pharmaceutical companies, and nonprofit organizations such as the Bill and Melinda Gates Foundation. These research and development partnership are essential for advancing maternal immunization. Continued efforts are needed to promote maternal immunization to protect pregnant women and their infants against vaccine-preventable infectious disease, especially in resource-limited settings where the burden of infections is high.

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1. Introduction

Efforts at the National Institutes of Health (NIH) to protect mothers and their infants against infectious diseases have involved a bench-to-bedside approach. Basic and translational research has provided a foundation for clinical studies with investigational and licensed vaccines. These studies assessed the safety and immunogenicity of vaccines in pregnant women and their children. Additional research is ongoing which has the potential to impact maternal immunization by informing policy and product development.

While comprehensive review of each study supported over the past 35 years would have been one approach, the purpose of this review is to highlight several types of nonclinical and clinical studies that led to a better understanding of responses to vaccines administered during pregnancy. Selected NIH supported clinical trials are presented in Table 1.

At the National Institute of Allergy and Infectious Diseases (NIAID) all of the above efforts were funded via grants, contracts and interagency agreements with other government agencies. The breadth of the program is demonstrated by diversity of agents and products tested. Studies of vaccines to protect infants against infections caused by Streptococcus pneumoniae, group B Streptococcus (GBS), Bordetella pertussis, Haemophilus influenzae type b (Hib), respiratory syncytial virus (RSV), seasonal and pandemic influenza...
Table 1
Selected NIH vaccine studies in pregnant women and their infants.

<table>
<thead>
<tr>
<th>Vaccine target</th>
<th>Product</th>
<th>Population</th>
<th>Immunogenicity</th>
<th>Persistence of maternal antibodies in infant blood or relevant information if only infant sample was cord blood</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group B</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Streptococcus*</td>
<td>GBS III capsular polysaccharide vaccine</td>
<td>40 pregnant women</td>
<td>Immune response rate of 63%, comparable to a study with non-pregnant adults</td>
<td>3 months of age</td>
<td>[5]</td>
</tr>
<tr>
<td></td>
<td>GBS III-TT conjugate</td>
<td>30 pregnant women randomized 2:1 vaccine: saline placebo</td>
<td>Immune response in 95% comparable to non-pregnant women who received same dose and lot of vaccine</td>
<td>2 months of age</td>
<td>[7]</td>
</tr>
<tr>
<td>RSV*</td>
<td>RSV purified fusion protein-2 (PRF-2) vaccine</td>
<td>35 pregnant women randomized 4:3 vaccine: saline placebo</td>
<td>Immune response in vaccine recipients: 75% by Western Blot and 95% by ELISA</td>
<td>2 and 6 months of age</td>
<td>[2]</td>
</tr>
<tr>
<td>Pneumonia/Hib*</td>
<td><em>Haemophilus influenzae</em> type b conjugate (HbOC, HibTITER, Lederle Praxis Laboratories) and 23-valent pneumococcal polysaccharide vaccine (PSV, Pneumovax 23, Merck and Co)</td>
<td>60 pregnant women randomized 2:1 HbOC:PSV</td>
<td>Concentrations of maternal antibody to common pneumococcal serotypes were significantly higher at delivery in PVC immunized mothers versus HbOC immunized mothers</td>
<td>2 and 7 months of age (pneumococcal Ab, varied with serotype)</td>
<td>[10,11]</td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>9-valent pneumococcal conjugate vaccine (PVC-9, Wyeth Lederle)</td>
<td>152 pregnant women randomized 1:1 vaccine: saline placebo</td>
<td>Significantly higher type specific pneumococcal antibodies in mothers receiving PVC-9 compared to controls at delivery and 2, 6 and 13 months post vaccination</td>
<td>Immunization of mothers with PVC-9 correlated with decreased infant antibody responses to some vaccine serotypes (routine immunization with Prevnar)</td>
<td>[35]</td>
</tr>
<tr>
<td>Hib*</td>
<td>Capsular polysaccharide (PRP) vaccine of <em>Haemophilus influenzae</em> type b</td>
<td>213 pregnant women randomized to receive PRP or saline placebo Cord samples from 75 deliveries (35 from PRP group and 40 from placebo group)</td>
<td>Infants born to PRP recipients had significantly higher levels of antibody to PRP than infants born to placebo recipients</td>
<td>Estimated that infants of PRP recipients would be protected for average of 4 months compared to two months for infants from placebo controls</td>
<td>[8]</td>
</tr>
<tr>
<td>Hib*</td>
<td>Hib polysaccharide PRP (Hib-immune, Lederle Labs) Hib conjugate PRP-D (Pneomune, Connaught) Hib conjugate HBc (HibTITER, Lederle Praxis Laboratories)</td>
<td>50 pregnant women randomized to receive PRP [13]; PRP-D [19] and PRP-HbOC [18] 47 unimmunized pregnant women</td>
<td>Mothers who received any Hib vaccine had significantly higher anti-PRP antibodies than unimmunized women. Women who received Hib conjugate Hib vaccines had higher levels than women who receive PRP vaccine.</td>
<td>Protective PRP antibody level in cord specimens from all infants of immunized mothers compared with 60% of unimmunized controls.</td>
<td>[9]</td>
</tr>
<tr>
<td>Pertussis*</td>
<td>Adacel® (Sanofi Pasteur, Tdap) Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine</td>
<td>48 pregnant women randomized 2:1 vaccine: saline placebo with crossover immunization postpartum 32 age matched non-pregnant women (Tdap open label)</td>
<td>Significantly higher concentrations of pertussis antibodies at birth and 2 months of age following antepartum versus postpartum vaccination.</td>
<td>2 months of age</td>
<td>Pertussis antibody responses in infants born to women receiving Tdap during pregnancy were not different following the fourth dose of DTaP</td>
</tr>
<tr>
<td>Trivalent influenza*</td>
<td>Trivalent influenza vaccine (TIV) (Connaught Laboratories) Tetanus toxoid vaccine (TT) (Connaught Laboratories)</td>
<td>30 pregnant women randomized 1:1 TIV:TT</td>
<td>Maternal seroconversion to one or more vaccine antigens in all TIV recipients and 9/13 TT recipients</td>
<td>2 months of age</td>
<td>[36]</td>
</tr>
<tr>
<td>Trivalent influenza*</td>
<td>Trivalent Influenza vaccines and monovalent H1N1 administered as part of routine clinical care</td>
<td>239 pregnant and postpartum women Observational cohort 4 consecutive influenza vaccination seasons</td>
<td>Adequate seroconversion rates demonstrated during pregnancy and postpartum period. Seroconversion rates lowest in first trimester (54.8%) and immediate postpartum (54.8%) and highest in late third trimester (69.6%) and late postpartum (69.4%).</td>
<td>Not applicable as no infant blood samples collected.</td>
<td>[37]</td>
</tr>
</tbody>
</table>
and human immunodeficiency virus type 1 (HIV) have been sponsored. The largest number of volunteers participated in studies conducted in response to the H1N1 influenza pandemic in 2009 when there was a critical need to evaluate monovalent vaccines in pregnant women.

A priority moving forward will be to determine lessons learned from completed maternal immunization studies in order to inform and improve future endeavors. To accomplish this goal, collaborations have been initiated with the US Food and Drug Administration (FDA), the Bill and Melinda Gates Foundation (BMGF), PATH (formerly known as Program for Appropriate Technology in Health), the World Health Organization (WHO), and the US Centers for Disease Control and Prevention (CDC) to support and publish the proceedings of conferences focused on maternal immunization topics (Fig. 1). These proceedings (see Section 4) inform the public health community about the safety of immunizing pregnant women, and the potential of vaccine immune responses to protect mothers and their infants against infectious diseases. Collaborations with FDA have included discussions on preclinical, laboratory, clinical and regulatory issues. Partnerships with pharmaceutical companies have provided assistance for the evaluation of their vaccines in pregnant women. This approach is expected to improve uptake of recommended vaccines in pregnancy in the United States, and to encourage maternal immunization efforts in low and middle income countries where there is an extremely high burden of infectious diseases in infants.

2. Basic and translational studies

Some examples of this bench to bedside strategy that moved basic research identifying potential antigens into preclinical and early translational studies are described in Table 2 and the sections that follow. These and similar studies funded by NIH paved the way for vaccine trials in pregnant women.

2.1. Natural history studies

Natural history and epidemiology studies identified background rates of expected adverse events (AEs), correlates of natural protection and potential impact of maternal immunization on disease epidemiology.

### Table 1 (Continued)

<table>
<thead>
<tr>
<th>Vaccine target</th>
<th>Population</th>
<th>Immunogenicity</th>
<th>Persistence of maternal antibodies in infant blood or relevant information if only infant sample was cord blood</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trivalent influenza*</td>
<td>2008/2009 trivalent influenza vaccine Fluzone® (Sanofi Pasteur) Fluarex® (GlaxoSmithKline) H1N1 vaccine hemagglutinin (HA) (Sanofi Pasteur)</td>
<td>102 pregnant women randomized 1:1 Fluzone:Fluarix</td>
<td>Immune responses similar to those achieved in non-pregnant women.</td>
<td>Not applicable as no infant blood samples were collected.</td>
</tr>
<tr>
<td>2009 H1N1*</td>
<td>120 pregnant women randomized 1:1 to 2 doses of 25 μg or 2 doses of 49 μg HA administered 21 days apart</td>
<td>One dose of vaccine was highly immunogenic with 91% seroprotection after one dose of 25 μg HA and 97% seroprotection after one dose of 49 μg HA</td>
<td>Not applicable as only infant sample collected was cord blood.</td>
<td></td>
</tr>
<tr>
<td>2009 H1N14</td>
<td>127 pregnant HIV infected women on antiretroviral therapy received 2 doses administered 21 days apart</td>
<td>Moderately immunogenic with 73% seroprotection after first 30 μg dose and 80% after second dose (less immunogenic than in studies with HIV-uninfected pregnant women)</td>
<td>Seroprotection in infants waned rapidly: 65% at delivery, 26% at 3 months and 12% at 6 months</td>
<td></td>
</tr>
</tbody>
</table>

Safety objective: No safety signal in any of the studies.
Immunogenicity objective: Efficient transplacental transfer of antibodies from mother to infant and persistence.
NIH sponsor: a = DMID, b = NIDCD, c = DAIT, d = DAIDS and NICHID.
Ab-antibody.
the beginning and end of the infants’ first RSV season. Infants were actively monitored for acute respiratory illness at intervals consistent with previous studies. Nasal specimens were processed with methods established in the surveillance studies to confirm RSV disease. The vaccine was well tolerated and immunogenic in mothers, and antibodies were transferred to the infants without enhancement of RSV disease.

Several GBS studies funded by DMID have generated data that will influence maternal immunization as a prevention strategy. A case-control study of mothers and their infants with early onset GBS disease versus mothers of healthy infants was conducted in 1998–1999 in Houston, Pittsburgh, and Seattle. Levels of maternal GBS capsular polysaccharide-specific antibody measured in maternal serum demonstrated that concentrations of >1 μg/mL at the time of delivery appeared to protect most neonates from early onset GBS type Ia and III disease [3]. This correlate of protection is important to guide GBS vaccine development as vaccines move forward to licensure.

A longitudinal cohort study of non-pregnant women was conducted to investigate factors associated with vaginal and rectal-only acquisition of GBS [4]. Antibody data from this study led to a GBS type III-TT (tetanus toxoid) conjugate vaccine clinical trial in non-pregnant women to determine the effect of vaccination on GBS colonization. The vaccine significantly delayed the acquisition of vaginal GBS III colonization and rectal colonization. These data indicate vaccination of pregnant women as a potential strategy for preventing GBS colonization in the vagina and rectum (personal communication). Thus, prevention of GBS colonization in pregnant women could be an approach to protecting infants from GBS disease.

2.2. Vaccine antigen identification

Bacterial capsule polysaccharides (CPS) have been recognized as virulence factors that play an important role in pathogenesis. GBS vaccine development at NIAID was focused on CPS antigens. Basic research to elucidate the chemistry of these polysaccharides resulted in the identification of distinct, antigenically unique CPS structures for the serotypes associated with GBS disease. Early vaccines were prepared using native CPS. In the mid-1980s, pregnant women were immunized with a GBS type III CPS [5]. Because this vaccine was variably immunogenic, conjugate vaccines were developed. Non-pregnant women immunized with a type III GBS CPS-TT conjugate vaccine demonstrated enhanced immunogenicity as compared to uncoupled CPS [6]. In a phase 1 randomized, double-blind, placebo-controlled clinical trial in pregnant women, the type III GBS CPS-TT conjugate vaccine elicited good levels of vaccine-specific antibody that was functionally active against type III GBS [7].

Vaccines to protect against Hib had a similar development path. At the National Institute of Child Health and Human Development (NICHD) early Hib polysaccharide vaccines were first developed and subsequently efforts continued to develop a polysaccharide-conjugate vaccines to protect against Hib infections. Hib conjugate vaccines and/or polysaccharide vaccines were administered to pregnant women [8–11]. The vaccines used in these studies were purified Hib polysaccharide polyribosylphosphate (PRP) conjugated to diphtheria toxoid (PRP-D) and PRP conjugated to a nontoxic mutant protein of diphtheria toxin (Hemophilus type b conjugate – diphtheria CRM 197 protein conjugate vaccine [HbDGC]).

NIH Small Business Innovation Research (SBIR) and Small Business Technology Transfer (SBT) grants4 provide funds to support research focused on new technologies that have potential for commercial products. Biotechnology companies funded by this mechanism are exploring new antigens/technologies for vaccine development which may progress to vaccines for maternal immunization studies.

2.3. Laboratory assays and reagents

Laboratory tests are critical for the advancement of vaccine candidates through the preclinical and clinical steps along the maternal immunization research pathway to support vaccine efficacy. Overall, this includes well-defined, optimized procedures for immunoassays, and the isolation and characterization of bacteria and viruses. Serologic assays are needed to evaluate antibody responses to vaccine candidates in basic research, animal models and clinical studies, and to measure antibodies in sero-epidemiological studies. Serologic assays used in toxicology studies support vaccine safety. Although blood is the most common sample to be tested, antibodies in breast milk were evaluated in several maternal immunization studies.

For example, DMID has supported the development of laboratory methods used in maternal immunization efforts related to GBS, influenza, RSV, Hib, pertussis and S. pneumoniae research. For GBS studies, the spectrum of work included optimizing recovery of GBS from clinical specimens [12], characterizing GBS isolates [13] and measuring the concentration and functionality of GBS CPS-specific antibodies [14,15]. For H1N1 influenza vaccine studies Southern Research Institute developed serologic assays that allowed comparisons of concentration and functionality of antibodies between trials of influenza vaccines in pregnant women and healthy young adults. For the RSV maternal immunization study, procedures were developed for isolating and identifying RSV from clinical samples, measuring vaccine-induced antibodies in blood and breast milk, and distinguishing immune responses of the vaccine from RSV infection by Western Blot analysis [2,16]. For the Hib and S. pneumoniae maternal immunization studies, DMID funded the development of immunoassays to measure concentration and functionality and used them to test clinical samples [10,17,18]. Recently, a new human pneumococcal standard reference serum (007), a critical reagent used in pneumococcal immunoassays, was prepared with support from NIAID and the Center for Biologics and Evaluation Research (CBER) at the FDA [19].

For the pertussis maternal immunization study [20], serologic assays were conducted in collaboration with Sanofi Pasteur. Studies to develop assays to test cell-mediated and humoral antibodies for

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2. The standard 007sp can be obtained from FDA by contacting Mustafa Akkyounlu, MD PhD at the FDA/CBER/OVRR/DBPAP/Laboratory of Bacterial Polysaccharides. Email: Mustafa.Akkyounlu@fda.hhs.gov.

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immune profiling of response to whole cell and acellular pertussis vaccines are ongoing.5

RSV reagents including strains, human reference sera and cotton rat reagents are provided without charge to the research community. The following items have been requested by academic investigators, companies and research foundations to support vaccine development efforts: (i) RSV A-2 and RSV B-1, well-characterized strains manufactured at Walter Reed Army Institute of Research, funded by an interagency agreement between NIAID and the Department of Defense; (ii) RSV reference serum prepared by Wyeth [21] and partially funded by NIAID; (iii) RSV reference immune globulin prepared by Baxter and an anti-RSV panel [22] developed through an interagency agreement between NIAID and CBER; and (iv) cotton rat reagents.6 Although the cotton rat is considered the animal model of choice for RSV studies, its use in biomedical research had been limited because of the lack of species-specific reagents. The current availability of cotton rat reagents has provided an important tool for RSV vaccine development for the study of mechanisms of disease pathogenesis and immunity.

2.4. Maternal immunization animal models

The baboon has emerged as an excellent nonhuman primate model to evaluate maternal immunization. For RSV [23] and pertussis [24], infected infant baboons develop clinical manifestations that parallel those in human infants. Maternal immunization studies with baboons have been conducted using Hib [25], pertussis [26] and RSV [27] vaccines. In some studies, female baboons were primed with the study vaccine before pregnancy to mimic the human experience. In all studies, females were vaccinated during pregnancy. In addition to assessing the immune response following maternal immunization, recent studies included infection of newborn animals with live pathogens [26,27]. Endpoints included measurement of the immune response following vaccination and protection of the newborn animals against clinical disease following infection. An immune response was detected in mothers following vaccination [25–27] and offspring of vaccinated mothers were protected against infection [26,27]. These results have led to the use of the baboon maternal immunization model to evaluate a new RSV vaccine candidate [28].

The baboon model has also been used to evaluate the immunogenicity of a GBS III-TT vaccine [29]. As new GBS vaccine candidates become available, this model could be used to study parameters of maternal immunization, such as immunogenicity when administered to pregnant baboons and transfer of polysaccharide-specific antibodies to infants.

2.5. IND-enabling studies

Studies in pregnant women in the United States must be conducted under an Investigational New Drug Application (IND) which requires documentation that the sponsor has complied with all requirements in 21 Code of Federal Regulations, Part 312. Developmental toxicity studies in animals are required as part of the IND application and must demonstrate no fetal toxicity for vaccines to move forward to testing in pregnant women. Dr. Pamela McInnes (then at DMID/NIAID, and currently deputy director of the National Center for Advancing Translational Sciences (NCATS) and CBER/FDA staff collaboratively developed protocols for developmental toxicity studies in rabbits which have been used for GBS

III-TT vaccine, Hib vaccine, pneumococcal polysaccharide vaccine, pneumococcal conjugate vaccine, and RSV PRP-2 subunit vaccine. Results of these studies indicated no reproductive safety signal in vaccinated animals. A description of the developmental toxicity study performed with GBS III-TT has been published [30].

3. Clinical studies

3.1. NIH support of maternal immunization studies

Early studies evaluating vaccines in pregnant women were funded by various NIH contracts supporting programmatic research (e.g., CBS, respiratory pathogens). In 1991, a contract was awarded to the Baylor College of Medicine for a Maternal Immunization Group. More recent maternal immunization studies were performed through Vaccine and Treatment Evaluation Units (VTEUs) which are supported by NIAID contracts. The VTEUs, a nationwide group of institutions that was established in 1962, have generated data to affect policy regarding important public health issues.7 When the 2009 H1N1 influenza pandemic emerged, the VTEUs were contacted to evaluate safety and the immune response to various dosing regimens of candidate vaccines in pregnant women (Table 1). The results of these vaccine trials were made available within a few months to help public health officials determine the most appropriate dose of vaccine for this vulnerable population.

The Division of AIDS (DAIDS) at NIAID has supported clinical networks to conduct vaccine trials in individuals with or at risk for HIV infection. Currently, NIAID and NICHD fund a network enrolling HIV-infected pregnant women as well as HIV-infected or –exposed children in various clinical studies (the International Maternal Pediatric Adolescent AIDS Clinical Trials Network [IMPAACT]).8 This network supported a clinical trial of the 2009 H1N1 influenza vaccine in HIV-infected pregnant women [31].

At DMID, a key to success of the maternal immunization program has been the management of vaccine trials by a protocol team with a scientific lead, a clinical trials specialist, a regulatory affairs specialist and a medical monitor who worked together with academia and industry. The scientific lead is a program officer responsible for the planning, implementation and monitoring of the vaccine trials. The clinical trials specialist works with the protocol team and investigators to ensure that good clinical practices are followed during the vaccine trial, which includes scheduling of clinical monitoring at clinical sites, and often serving as a communications liaison between DMID, the clinical site(s) and industry partners. The regulatory affairs specialist is responsible for IND submissions to the FDA and coordinating responses to FDA inquiries with other members of the protocol team. The medical monitor manages safety monitoring activities for the vaccine trial, including but not limited to, scheduling data safety monitoring board or safety monitoring committee meetings.

3.2. Maternal immunization protocol development

Vaccines must be evaluated in non-pregnant women of childbearing age and shown to be safe prior to immunizing pregnant women. Investigational and licensed vaccines have been evaluated in NIAID-supported maternal immunization trials. The GBS III-TT vaccine is an example of an investigational vaccine that was first tested in non-pregnant women [6], found to be safe, and then administered to pregnant women [7].


6 These RSV reagents are available by direct request to BEI Resources (https://www.beiresources.org).

7 http://www.niaid.nih.gov/about/organization/dmid/researchers/clinical/vteu/ Pages/default.aspx.

8 http://impaaactnetwork.org/.
Protocol design for studies with pregnant women has evolved over time. DMID standard protocol templates were modified in regards to inclusion/exclusion criteria and safety assessment of mothers and their infants. For example:

- An obstetric eligibility algorithm used in early studies was revised as the American College of Obstetricians and Gynecologists (ACOG) updated recommendations for prenatal testing.
- Prior to 2009, women were enrolled at 30–34 weeks gestation. However, for influenza vaccine studies conducted in 2009, enrollment was extended to include women in their second trimester of pregnancy because of the Advisory Committee on Immunization Practices (ACIP) recommendation that all pregnant women be immunized with influenza vaccine.
- In most studies, pregnant women were randomized to receive the vaccine under investigation, or an alternative vaccine or placebo. Occasionally, a non-pregnant group of women was included as an additional control group [20].
- Pregnancy-specific toxicity tables for vital signs, laboratory values and safety assessments of mothers and infants were developed by a panel of experts as new data were collected and reviewed [32–34].
- A maternal immunization protocol development meeting concluded that in addition to growth (weight, height and head circumference) different aspects of infant’s neurodevelopment (motor, social, language) should be assessed during the follow up. In an effort to assess neurodevelopment various tests were used in DMID protocols: Bayley III [20], Iretton [35] and Denver Development tests (2 and 7). Although no problems were found using these testing procedures, it was unclear which test was most appropriate. Infant development experts were consulted, and the consensus was that Bayley III tests were the most standardized but results are not definitive until 18–24 months of age. However, as a practical matter, the latest infant assessment visit in most maternal immunization studies has generally been at six or 12 months of age. Depending on a study and the vaccine some infants were followed up to two years of age.

3.3. Maternal immunization protocol objectives

Most DMID-supported maternal immunization studies were phase II proof of concept trials with evaluation of safety as the highest priority. Thus the primary objective was to evaluate systemic and local reactogenicity. No safety signal has been detected in any of these clinical trials in pregnant women.

Secondary objectives include evaluating immunogenicity using appropriate methods (e.g., enzyme-linked immunosorbent assay [ELISA], opsonophagocytosis killing, viral neutralization). At a minimum, immunogenicity is evaluated by measuring vaccine specific antibodies in blood samples taken from pregnant women before and 3–4 weeks after vaccination. Transplacental transfer of maternal antibody is determined by comparing the amount of vaccine-specific antibody in the mother’s blood at the time of delivery to the amount in infant cord blood. Efficient transplacental transfer has been found in all studies to date that collected paired maternal and umbilical cord blood samples. Persistence of maternal antibody is determined by measuring vaccine-specific antibody in infant serum samples collected after delivery, usually at two and six months of age. Persistence has been observed at protocol specific time intervals in all studies assessing it. In some clinical trials, breast milk samples were collected from immunized mothers and vaccine-specific antibody documented [2,10].

Additional (usually exploratory) outcome measures included the effect of maternal immunization on clinical illness in infants born to vaccinated mothers and the effect of maternal immunization on infant immune responses to recommended routine vaccines (see Table 1).

Additional examples of some study specific objectives and findings are listed below:

- In a clinical trial administering RSV FFP-2 vaccine to pregnant women, infants were followed through the first RSV season after birth. RSV disease was confirmed by culture and/or serology. There was no evidence of increased frequency or severity of RSV256 associated illness in infants from vaccine recipients when compared to controls [2].
- Lower levels of pneumococcal nasal colonization were detected in infants of mothers immunized with 23-valent pneumococcal polysaccharide vaccine as compared to infants of mothers immunized with HbOC [10].
- Infants born to mothers who had received a pneumococcal 9-valent vaccine were more likely to have otitis media (OM) in the first six months of life than those whose mothers received placebo. This difference in OM rates did not persist beyond six months of age. High levels of maternal pneumococcal antibody at birth may have suppressed early infant response to their pneumococcal conjugate vaccine-7 (PCV-7) immunization (Prevnar), resulting in OM [35].
- In a maternal immunization study with pertussis vaccine (Adacel), there were slightly decreased immune responses following the primary infant series of pertussis immunizations (Pentacel) compared to controls, but differences did not persist following the booster [20].

3.4. Influenza vaccine protocols

Numerous influenza vaccine studies were conducted in pregnant and postpartum women (Table 1). These studies evaluated reactogenicity and immunogenicity of influenza vaccines in a number of ways: comparing them to other vaccines (TT [36]); to the vaccines administered in consecutive seasons, or postpartum [37] or comparing different formulations [38].

In the fall of 2009, as soon as monovalent H1N1 vaccines were available and initial safety data obtained in healthy adults, maternal immunization studies were initiated. In these studies, pregnant women were randomized to receive different vaccine dosages to determine the optimal regimen. Studies with 2009 H1N1 vaccines were conducted in healthy pregnant women [39,40] and HIV-infected pregnant women [31]. In all these NIH funded studies the influenza vaccines tested in pregnant women were found to be safe and immunogenic.

4. Meetings, workshops and other collaborative efforts to advance maternal immunization

As part of the integrated efforts to advance maternal immunization strategies, NIH uses input from public workshop and other forums to assist in building a consensus approach. The first NIAID workshop on maternal immunization was held in 1989 [41]. The purpose was to review the safety, immunogenicity, efficacy and acceptability of immunizations administered to pregnant women to prevent maternal disease during late pregnancy and to prevent disease in early infancy.

The Office of Research on Women’s Health (ORWH) was established in 1990 by Congressional mandate to promote women’s health research within and beyond the NIH scientific community. This office held a workshop in 2011 considering barriers and opportunities in conducting clinical research studies enrolling pregnant women [42].

Recent national initiatives to promote and advance maternal immunization include a meeting in 2011 organized by the National
Vaccine Program Office (NVPO), Department of Health and Human Services (DHHS), to assess progress in overcoming barriers to immunizing pregnant women with influenza vaccines and to prioritize research and programmatic efforts. Co-sponsors included ACOG, CDC, FDA and NIAID. Proceedings were published in a special issue of the American Journal of Obstetrics and Gynecology [43]. In 2011 and 2012, DMID organized a series of conferences to review data from previous trials. The discussions resulted in standardization of reference values for vital signs and laboratory assessments [32], and consensus related to safety assessments for mothers and infants [33,34] which will be incorporated into future maternal immunization protocols.

DMID convened follow-up meetings in 2013 to discuss barriers to and opportunities for research in pregnancy including, but not limited to, design of pharmacokinetics (PK) studies during pregnancy, recruitment and retention of pregnant women in clinical trials, and reporting of congenital anomalies. Executive summaries from these conferences were published as a supplement to Clinical Infectious Diseases (CID) funded by the BMGF [44]. In 2014, a symposium was devoted to global health and specific aspects of research during pregnancy in low and medium income countries. The majority of information appearing in this special issue of Vaccine was presented at the conference in 2014. An RSV Vaccine Workshop, in June 2015, was co-sponsored by CBER and DMID which included a session on the development of RSV vaccines for use in pregnancy.

In addition to organizing conferences and workshops, NIH staff have participated in and presented at conferences and workshops organized by FDA, CDC, NVPO, ACOG, the March of Dimes, and the BMGF which have been extremely helpful in identifying unresolved issues and building consensus. For example, NIH staff are actively involved in the National Vaccine Advisory Committee’s (NVAC’s) Maternal Immunization Working Group. DHHS, NVAC recently reviewed the current state of maternal immunization in the US and formulated specific recommendations to the Assistant Secretary of Health in a report adopted by NVAC in 2014 [45].

5. Conclusion

NIH has been supporting maternal immunization studies for over 35 years. Basic and translational research provided a strong foundation for clinical studies. No safety signals have been detected in any of the studies to date. In multiple studies, the immune response to the vaccine was measured and efficient transplacental transfer was documented, indicating potential protection of mothers and their neonates. NIH staff and collaborative partners responded rapidly to the H1N1 pandemic by initiating clinical trials with pregnant women as soon as vaccines were available. These completed studies were able to quickly provide data for policy decisions. By working together with other institutes and offices at NIH, DHHS agencies and offices (FDA, CDC, NVPO), WHO, pharmaceutical and biotechnology companies, and non-profit organizations, there is increased awareness regarding the benefits of maternal immunization. Continued efforts are needed to promote maternal immunization to protect pregnant women and their infants against vaccine-preventable infectious diseases, especially in resource-limited settings where the burden is high.

In summary, research and development efforts are essential for advancing maternal immunization as a strategy for disease prevention in pregnant women and their infants.

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