Global and National Initiatives to Facilitate Studies of Vaccines in Pregnant Women

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Keywords. vaccines; pregnancy; maternal immunization; pregnancy labeling.

Vaccination of pregnant women can protect women and newborn infants against certain infectious diseases, as evidenced by the success of maternal tetanus vaccination programs [1, 2]. There has been recent renewed interest and focus on maternal immunization, defined in this article as vaccination of pregnant women, as a means to protect the mother and young infants from additional vaccine-preventable diseases. For example, because of increased morbidity associated with influenza during pregnancy, inactivated influenza vaccines are now recommended for use in women during all stages of pregnancy in numerous countries [3, 4]. In addition, tetanus, diphtheria, and acellular pertussis vaccines have been recommended recently for pregnant women in an effort to reduce the burden of pertussis in infants [5, 6]. Other maternal immunization strategies to protect the fetus, the newborn, and the infant from infectious diseases not preventable by current vaccination strategies are in development and include vaccines against cytomegalovirus, respiratory syncytial virus, and group B Streptococcus (GBS) [7–9].

Implementation of maternal vaccination programs has been poor or modest in many countries [10–12]. This is due to several reasons including lack of safety and effectiveness data obtained in pregnant women for specific vaccines, theoretical concerns about fetal risk from vaccination of pregnant women, manufacturers’ liability concerns, and practical barriers such as a lack of infrastructure for storing vaccines in antenatal clinics. For maternal immunization programs to be successfully implemented, overcoming these perceived and real obstacles is important. A number of global and national initiatives to promote and facilitate maternal immunization are under way and are summarized in this article. Although the majority of these initiatives focus on maternal immunization with inactivated influenza vaccines, the concepts are applicable to other vaccines that are either currently in development or recommended by public health bodies for use in pregnant women.

In recent years, growing interest in maternal immunization has been evident in the activities of both public and private entities concerned with international public health. In 2012, the World Health Organization (WHO) recommended that pregnant women have the highest priority for seasonal influenza vaccination in countries considering the initiation or expansion of influenza immunization programs [4]. The recommendation was based on a review of burden of influenza disease, influenza vaccine safety, and influenza vaccine effectiveness by the WHO Strategic Advisory Group of Experts on Immunization (SAGE) [13]. In 2012, the WHO Global Advisory Committee on Vaccine Safety evaluated data from interventional and noninterventional studies and spontaneous reporting systems derived from vaccination of pregnant women with a number of viral, bacterial, toxoid, and live attenuated vaccines. The Committee concluded that there is no evidence of adverse pregnancy outcomes from vaccinating pregnant women with inactivated viral, bacterial, or toxoid vaccine [14]. Based on a meeting in 2013, convened to devise methods to promote maternal immunization and...
identify barriers, SAGE concluded that recommending advisory bodies as well as WHO should quantify and communicate risk-benefit considerations for maternal immunization and engage with regulators and manufacturers to address barriers to maternal immunization programs [15].

In 2011, the Bill & Melinda Gates Foundation (BMGF) convened an international consultation to discuss the potential for maternal influenza immunization in resource-limited settings and to identify gaps and necessary approaches to facilitate the implementation of maternal influenza immunization programs. Topics of discussion included scientific, regulatory, legal, programmatic, and funding issues, as well as review of available safety and effectiveness data derived from studies in women administered influenza vaccines during pregnancy. Attendees concluded that data from immunogenicity studies and clinical effectiveness trials of trivalent inactivated influenza vaccine in pregnant women support recommendations for immunization of pregnant women with inactivated influenza vaccine to protect the mother from influenza disease. It was acknowledged that additional data to assess the benefit to the newborn infant are necessary to assist countries in prioritizing maternal immunization programs [16]. In response to this consultation, the BMGF awarded a grant to WHO and PATH to execute the “Maternal Influenza Immunization Project” to implement seasonal influenza immunization programs for pregnant women and to pave the way for expanded maternal immunization programs that, in the future, may include vaccines currently under development [12].

In 2012, the Global Vaccine Action Plan (GVAP) was approved by the World Health Assembly and is a framework to achieve the Decade of Vaccines vision by delivering universal access to immunization [17]. One of the objectives of GVAP is to create strategies for reaching individuals throughout their life and includes use of vaccines during pregnancy [18]. In 2014, the Global Vaccine and Immunization Research Forum co-sponsored by the WHO, the National Institutes of Health (NIH), and the BMGF discussed progress made under the GVAP including maternal immunization programs. At that forum, BMGF presented its maternal immunization platform targeting 5 diseases: influenza, respiratory syncytial virus, pertussis, GBS, and tetanus [19]. BMGF funded 3 clinical studies in Mali, Nepal, and South Africa to evaluate the safety and efficacy of influenza vaccines administered during pregnancy with the goal to protect women and infants from influenza [20].

Additional maternal immunization forums in recent years include a meeting convened by the Fondation Mérieux in September 2012 that brought together international experts from academia, industry, and regulatory agencies to discuss the risks and benefits of immunization during pregnancy, legal and liability issues, and regulatory requirements, as well as safety surveillance [21]. Attendees concluded that vaccines recommended for use in pregnancy should be provided to and by practitioners, with minimal barriers. Attendees recognized the need for additional studies to generate surveillance data (eg, burden of disease, safety and effectiveness of vaccines administered in pregnancy) as well as additional data on vaccine-induced maternal immunogenicity. In addition, studies assessing potential maternal antibody interference with the infant’s immune response to the same or similar vaccines were recommended, as well as studies to evaluate the safety of vaccines and effectiveness in various populations and settings. The need for operational research in different regions of the world to determine the feasibility and cost of delivering vaccines to pregnant women was stressed. It was recommended that public health agencies lead these efforts.

There also have been recent national US initiatives to foster maternal immunization. For example, a meeting was held in October 2011 in Rockville, Maryland, that was sponsored by the National Vaccine Program Office with the objectives to assess progress in overcoming barriers to immunizing pregnant women with influenza vaccines in the United States and to prioritize research and programmatic efforts. Presentations included review of available safety and effectiveness data of influenza vaccines administered during pregnancy, US postlicensure surveillance systems that are used to monitor the safety of vaccines administered during pregnancy, US regulatory requirements, liability issues related to immunization of pregnant women, and patient and provider barriers to influenza immunization. Topics discussed and outcomes were published in a special issue of the American Journal of Obstetrics and Gynecology [22].

The US 2010 National Vaccine Plan underscores the need to advance the science of neonatal and maternal immunity. To facilitate the development of a US national maternal immunization program, the Assistant Secretary for Health charged the National Vaccine Advisory Committee (NVAC) with reviewing the current state of maternal immunization in the United States and to identify gaps and obstacles to the implementation of current Advisory Committee on Immunization Practices recommendations regarding immunization during pregnancy [23]. The NVAC Maternal Immunization Working Group identified the following 5 major areas to increase uptake of recommended vaccines in pregnant women: (1) enhancing communication regarding the safety and effectiveness of all currently recommended immunizations during pregnancy; (2) maximizing obstetric provider recommendation and administration of recommended maternal immunization; (3) focusing efforts to improve financing for immunization services during pregnancy and postpartum; (4) supporting efforts to increase the use of electronic health records and immunization information systems associated with obstetrical care; and (5) recognizing and addressing current legal liability barriers to optimize clinical investigations and uptake of currently recommended and future vaccines during
pregnancy. Within each of these areas, the NVAC formulated specific recommendations published in a report that was adopted by NVAC on 11 June 2014 [24].

Studies of vaccines administered to pregnant women have been conducted or are ongoing under US Investigational Drug Applications held by the National Institute of Allergy and Infectious Diseases (NIAID) of the NIH or industry. The emergence of the 2009 H1N1 pandemic virus and evidence that this disease was more severe in pregnant women facilitated the initiation of studies of inactivated influenza vaccines in pregnant women by NIAID. Other vaccines evaluated by NIAID in pregnant women include GBS and Bordetella pertussis vaccines [20]. A GBS vaccine under clinical development by industry is intended for use in pregnant women to protect newborn infants [25].

The US Food and Drug Administration (FDA) has launched several initiatives to address use of drugs and biological products, including vaccines, in pregnancy. Current regulations prescribe that, with some exceptions, a pregnancy subsection must be included in labeling whereby each product is classified under 1 of 5 pregnancy categories on the basis of risk of reproductive and developmental adverse effect or on the basis of risk weighed against potential benefit [26]. With few exceptions, US-licensed vaccines are labeled either category B or C allowing vaccination of pregnant women if the benefits from use of the vaccine may be acceptable despite potential risk and when it is determined that the vaccine is clearly needed. Because of concerns expressed by the healthcare community that current information in the pregnancy subsection of the labeling is not sufficient to allow an informed decision of drug usage during pregnancy, the FDA engaged in a major initiative to revise current pregnancy labeling regulations [27]. Importantly, these new regulations, when implemented, would require that labeling include relevant available clinical information from use of the vaccine in pregnant women to help inform prescribing decisions and counseling of women about the use of the product during pregnancy and lactation.

In general, data from use of vaccines during pregnancy have been derived from postmarketing studies and/or maternal immunization studies published in the literature. These data usually inform recommendations about the use of the vaccine in pregnant women. Of note, the FDA has initiated a program to evaluate the feasibility of conducting surveillance for pregnancy outcomes after vaccination under its postlicensure rapid immunization safety monitoring program (PRISM), which is part of the FDA’s Sentinel Initiative. Building upon the existing PRISM framework, the FDA proposed to (1) augment the current PRISM data infrastructure to evaluate potential associations between vaccine exposure of pregnant women and adverse events occurring in mothers and infants and (2) develop the methodological framework for evaluating the potential risk for birth defects following vaccine exposure within PRISM. A final draft PRISM surveillance protocol entitled “Influenza Vaccines and Birth Outcomes” has been published [28]. Also, the FDA held a meeting in May 2014 to seek input from industry, academia, public health agencies, the clinical community and other stakeholders regarding designing and implementing pregnancy registries and to explore other methods of evaluating the safety of drugs and biological products, including vaccines, in pregnant women in the postlicensure setting. At this meeting, FDA also sought input on best practices to communicate information to patients and healthcare providers about pregnancy registries and other studies in which pregnant women can enroll [29].

From a US FDA regulatory perspective, prelicensure maternal immunization studies to evaluate the effectiveness of a vaccine used in pregnancy are needed for the prescribing information to include an indication and usage statement that specifically addresses use in pregnancy. For biological products, including vaccines, all indications must be supported by substantial evidence of effectiveness. The FDA generally accepts that such evidence is based on adequate and well-controlled studies. In addition, data demonstrating that the particular product is safe in the mother and the infant to support an indication of the vaccine during pregnancy would be needed. In the absence of such data, the prescribing information will lack an indication statement that addresses use in pregnancy. However, if the vaccine is not contraindicated, it may be used to immunize pregnant women if the benefits from the use of the vaccine in pregnant women are acceptable despite its potential risk and it is determined that the vaccine is clearly needed.

To facilitate both pre- and/or postlicensure studies in pregnant women, it is critical to develop a systematic approach to classifying adverse events observed in the mother and her infant, including grading and attribution of adverse events and defining relevant expected clinical and laboratory values. To address this, the Division of Microbiology and Infectious Diseases (DMID) at NIAID/NIH held a series of meetings in 2011–2012. The goal was to delineate a paradigm for designing and conducting immunization studies and antimicrobial investigations during pregnancy that would enable robust safety data generation [30]. In 2013, DMID/NIAID/NIH held an additional series of meetings entitled “Enrolling pregnant women in clinical trials of antimicrobials and vaccines” to extend and build on the work that was initiated in previous years. The working groups were charged with addressing the following 5 areas: (1) defining how birth defects should be assessed in future clinical trials of vaccines and antimicrobial drugs in pregnant women and available methods that could be used for the assessment of congenital anomalies; (2) evaluation of safety outcomes and adverse events among neonates whose mothers participated in clinical trials of antimicrobials and vaccines including developing
guidance with definitions of adverse events and grading tables specific for term and preterm infants; (3) recruitment and retention in clinical trials involving pregnant women; (4) design and implementation of pharmacokinetic and pharmacodynamic studies in pregnant women with a focus on antimicrobial agents; and (5) overcoming knowledge gaps in maternal immunization. This supplement to Clinical Infectious Diseases contains 5 companion papers authored by Rasmussen et al, Frew et al, Munoz et al, Beigi et al, and Sheffield et al, presenting the outcomes of these working group discussions. These articles may further contribute to enhancing recruitment and retention in clinical trials in pregnant women, improving design and conduct of maternal immunization trials, and facilitating use of standardized definitions and grading of safety outcomes in the pregnant mother and her baby that may ultimately serve to facilitate comparison of data across clinical trials.

Considerable progress has been achieved over the last decade with regard to maternal immunization programs. Maternal immunization studies have been completed or are ongoing to assess the safety and effectiveness of vaccines used in pregnancy. Barriers to maternal immunization programs are being assessed and addressed on a national and international scale to implement policies and procedures that support maternal vaccination. Regulators and vaccine manufacturers have engaged in a dialogue to agree on prelicensure maternal immunization trials. Postlicensure safety surveillance systems need to be developed and/or expanded on to assess the safety of the vaccine in the mother and her infant. Legal liability issues will need to be addressed. Finally, current efforts addressing gaps in knowledge and educational needs of both the pregnant mother and the healthcare professional are critical to inform the public about health benefits of vaccination during pregnancy to protect pregnant mothers, the fetus, and newborn infants from vaccine-preventable infectious diseases.

Notes

Supplement sponsorship. This article appears as part of the supplement “Including Pregnant Women in Clinical Trials of Antimicrobials and Vaccines,” sponsored by the Bill & Melinda Gates Foundation.

Potential conflict of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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