DRAFT Monday, August 22, 2016- In advance of a voting decision by the National Vaccine Advisory Committee

The National Vaccine Advisory Committee: Overcoming Barriers and Identifying Opportunities for Developing Maternal Immunizations

Executive Summary

Recognizing the importance and impact of maternal immunizations on public health, the Assistant Secretary for Health (ASH) charged the National Vaccine Advisory Committee (NVAC) in June 2012 with reviewing the state of maternal immunizations and existing best practices to identify programmatic gaps and/or barriers to the implementation of current recommendations regarding maternal immunization. The NVAC established the Maternal Immunization Working Group (MIWG) in August 2012 to conduct these assessments and provide recommendations for overcoming any identified barriers.

The report that follows reflects the work of the task group focused on identifying barriers to and opportunities for developing vaccines for pregnant women and make recommendations to overcome these barriers. The NVAC working group initially described four main focus areas on which to concentrate their efforts on. These included i) ethical issues; ii) policy issues; iii) pre-clinical and clinical research issues; and iv) provider education and support issues.

Focus Area 1: Ethical Issues

1.1 The Assistant Secretary for Health (ASH) should work with the Office of Human Research Subjects Protection (OHRP) and other relevant stakeholders and agencies to revise the current exclusionary climate of research in pregnancy. Such areas of focus include but are not limited to:

1.1.1 Institutional Review Board (IRB) guidance on interpretation of minimal risk

1.1.2 Code of Federal Regulations language surrounding research in pregnancy

1.1.3 Collaboration with bioethics experts, regulatory agencies, and the scientific community to optimize the design of studies to minimize the risk of interventions for research in pregnancy

1.1.4 Relevant regulations, statutes, and policies that should be modified to indicate that pregnant women are not a vulnerable population for the purposes of ethical review

1.2 The ASH should work with OHRP and the stakeholder community to develop policy and regulatory guidelines that would promote inclusion of pregnant women in clinical trials when scientifically appropriate

Focus Area 2: Policy Issues

2.1 The ASH should continue to support maternal immunization as an important public health strategy to encourage manufacturer investment in the development of new and currently licensed vaccines for additional indications for use specifically in pregnant women

2.2 The ASH should advocate to the Secretary of Health and Human Services to resolve the uncertainties around coverage under the Vaccine Injury Compensation Program (VICP) for vaccines administered to pregnant women that are not recommended for use in children by the Centers for Disease Control (CDC), and for liability protections for live-born infants born to mothers vaccinated during pregnancy

Focus Area 3: Pre-Clinical and Clinical Research Issues

3.1 The ASH should prioritize increased support for pre-clinical and early clinical research to understand the immune response during pregnancy and to develop vaccines for pregnant women:

3.1.1 The ASH should work with federal and non-federal stakeholders to create or promote mechanisms that support investigator-initiated and other types of research that fosters innovation and expands the field of vaccines for pregnant women

3.2 The ASH should emphasize the need for a better understanding of the public health burden of diseases preventable by maternal immunization

3.3 The ASH should work with CDC, NIH, and other relevant federal agencies to support evaluation of the maternal and neonatal outcomes of vaccines administered during pregnancy with respect to the (1) safety of vaccines and (2) effectiveness of vaccines to reduce maternal and infant morbidity and mortality caused by vaccine-preventable diseases, and (3) to better understand the potential risks and benefits of maternal immunization

3.4 The ASH should support continuing evaluation of vaccines in pregnant women and infants born to vaccinated mothers, while advocating for the adoption of standardized approaches to data collection, analysis, and safety evaluation

3.5 The ASH should support the adoption and utilization of standardized definitions of possible maternal and neonatal outcomes to evaluate the safety and effectiveness of vaccines administered during pregnancy

3.6 The ASH should convene stakeholders and other federal agencies to work on the expansion of pharmacovigilance systems that readily link maternal and infant electronic health records and safety surveillance systems

Focus Area 4: Provider Education and Support Issues

4.1 The ASH should encourage professional societies to continue to support the inclusion of pregnant women in clinical research

4.2 The ASH should work with relevant stakeholders to increase awareness among obstetric providers and pregnant women about the importance of vaccine research during pregnancy

4.3 The ASH should work with professional societies to educate obstetricians and other obstetric providers on vaccination and interpretation of new regulations regarding labelling (i.e., the Pregnancy and Lactation Labeling Rule) so they can make informed decisions and counsel their patients more effectively

Introduction

Infants are vulnerable to vaccine-preventable diseases during the first months of life due in part to the susceptibility gap that occurs when they are too young to be vaccinated but are still at a considerable risk of morbidity and mortality from those diseases. Early infancy, including the neonatal period or the first 28 days of life, is the most vulnerable time for childhood survival (UNICEF 2016). For example, the risk of influenza hospitalizations in infants less than six months of age is higher than in older children or elderly populations (Poehling, Edwards et al. 2006, Poehling, Edwards et al. 2013). And although infants are at a significantly higher risk of influenza-related complications, the available influenza vaccines are not licensed for use in infants less than six months of age. The lack of existing measures to protect infants from complications related to acquiring a disease for which a vaccine is available for older children represents a considerable gap that needs to be addressed. Immunizing pregnant women to allow for transplacental transfer of maternal antibodies to the infant who will thus be born with existing antibodies against vaccine-preventable diseases (e.g. influenza, pertussis, and tetanus) is a strategy that has been successfully used to reduce the burden of these diseases in infants in the United States (Steinhoff 2013). This has led to exploring the use of the same approach to shield infants from complications related to additional infectious diseases that could also be prevented by immunization (e.g. Respiratory Syncytial Virus and Group B Streptococcus) (Catlin 2008, Bizzarro, Shabanova et al. 2015, Kochanek, Murphy et al. 2016, Manuck, Rice et al. 2016).

Influenza. In the 1960s, the Advisory Committee on Immunization Practices (ACIP) managed by the Centers for Disease Control and Prevention (CDC) acknowledged the benefits of maternal influenza immunization both in preventing disease in the infant as well as in the mother. It was then that CDC first recommended that the influenza vaccine be administered to pregnant women who had high- risk medical conditions (Burney 1960). This recommendation was updated in 2004 for pregnant women to be vaccinated for influenza during all trimesters as well as women who would become pregnant during the influenza season (Fiore, Uyeki et al. 2010, National Center for and Respiratory 2011).

The coverage rate for the influenza vaccine administered during pregnancy since the recommendation was implemented has varied, but reached 47% after the H1N1 pandemic in 2009 (CDC 2012). More

recently, the CDC reported an increase in coverage up to 52.2% for the seasonal influenza vaccination in pregnant women for the 2013-2014 season (17.6% women received the vaccine before pregnancy and 34.6% during pregnancy) (Ding, Black et al. 2014), which has remained steady during the following seasons.

Maternal influenza vaccination has been an effective strategy used to protect infants less than six months of age from influenza-like illness and influenza-related hospitalizations. A retrospective study that included a cohort of 245,386 women and 249,387 infants demonstrated that infants who were born to vaccinated mothers had a reduced risk of 64% for influenza-like illness, 70% for laboratory-confirmed influenza, and 81% for influenza-related hospitalization within the first six months of life (Shakib, Korgenski et al. 2016). Similarly, other studies have also shown that maternal influenza vaccination is associated with an overall reduction in the incidence of hospitalization due to acute respiratory illness (regardless of etiology) among infants less than six months old (Regan, de Klerk et al. 2016). Preventing maternal influenza infection might additionally reduce the risk of the mother being the source of infection to the infant, and could also result in transmission of antibodies to the infant through breast milk (Schlaudecker, Steinhoff et al. 2013). Furthermore, some studies have suggested that influenza vaccination during pregnancy may have other indirect benefits such as a decrease in the rate of infants born small for gestational age, a decrease in the rate of preterm birth, and improvement upon other birth outcomes in some populations, but these findings have not been consistent among recent randomized clinical trials and observational studies (Omer, Goodman et al. 2011, Steinhoff, Omer et al. 2012, Richards, Hansen et al. 2013, Regan, de Klerk et al. 2016). In conclusion, these studies suggest that vaccinating pregnant women against influenza does not only protect the infant from influenza disease-like symptoms but may also provide additional health benefits for both the mother and the infant.

Pertussis. Infants are also exposed to other vaccine-preventable infectious diseases, such as pertussis (whooping cough). Infants have higher rates of pertussis infections than the rest of the population, and make up the largest burden of pertussis-related deaths, revealing the crucial need for providing protection against whooping cough during this stage (CDC 2011). CDC reported 3,159 cases of pertussis in infants less than six months of age between 2012 and 2013, compared to 892 cases of pertussis in infants 6-11 months of age (CDC 2015). In 2014 the majority of pertussis-related deaths also occurred among infants less than three months of age (CDC). Maternal immunization with the Tdap vaccine has

been shown to effectively protect infants, through the passive transfer of antibodies from the mother to the baby. Thus in 2012, CDC recommended the routine administration of a Tdap booster dose for pregnant women (CDC 2013), and further recommended that women should be re-vaccinated between 27 and 36 weeks of gestation with each subsequent pregnancy (CDC 2013). Although this recommendation has been implemented for a few years, the coverage for Tdap vaccination in pregnant women remains low. A recent observational study that included a cohort of 438,487 live births found that only 14% of the mothers received Tdap during pregnancy (Kharbanda, Vazquez-Benitez et al. 2016). Recent efforts by CDC and professional societies have helped increase Tdap rates in pregnant women to 41.7% as of 2013, but efforts are needed to continue to increase these rates (Kharbanda, Vazquez-Benitez et al. 2016).

Maternal Tdap administration has been shown to be both safe and immunogenic, as no acute maternal safety events or increased risks to the infant or mother have been reported to date (Munoz, Bond et al. 2014, Sukumaran, McCarthy et al. 2015, Sukumaran, McCarthy et al. 2015, Healy 2016, Kharbanda, Vazquez-Benitez et al. 2016). Infants in the United Kingdom born to mothers vaccinated with Tdap during pregnancy were less likely to have confirmed pertussis cases and more likely to have a reduction in pertussis-associated hospitalizations, demonstrating the effectiveness of Tdap immunization in decreasing infant disease (Amirthalingam, Andrews et al. 2014). Tdap immunization during pregnancy is also associated with achieving higher levels of pertussis antibodies in the infant, which remain present at two months of age (Munoz, Bond et al. 2014, Vilajeliu, Ferrer et al. 2016), and these high levels of pertussis antibodies in the cord blood have been correlated with protection against pertussis infection (Heininger, Riffelmann et al. 2013). These studies further validate the potential for maternal immunization as a strategy to protect infants from diseases such as pertussis.

Tetanus. The use of prenatal tetanus toxoid immunization is another example of how effective maternal immunization strategies have been in reducing the burden of infant disease (Steinhoff 2013). The implementation of a tetanus immunization program during pregnancy in countries where neonatal tetanus is an issue has resulted in a reduction of 94% in neonatal mortality (Schofield, Tucker et al. 1961, Blencowe, Lawn et al. 2010, Steinhoff 2013). Although neonatal tetanus is not a concern in the United States, the success of the implementation of maternal tetanus toxoid vaccination globally is another

great example of how immunizing pregnant women against vaccine-preventable diseases is an effective strategy to reduce and prevent disease in infants (Blencowe, Lawn et al. 2010, Steinhoff 2013).

Additional Targets for Maternal Immunization. There is also a great need for vaccines other than influenza and Tdap to be considered for administration to pregnant women to protect mothers and infants during the first months of life. The success of immunizing pregnant women against influenza has had such a positive outcome, that the same approach should certainly be attempted with immunizations against other diseases that put infants at risk. Relevant disease targets include vaccines against respiratory syncytial virus (RSV) and group B *Streptococcus* (GBS) (Beigi, Fortner et al. 2014, Abramson and Mason 2016), among others.

RSV infection often leads to viral pneumonia in infants less than two years of age and is responsible for high infant morbidity and mortality globally (Saso and Kampmann 2016). RSV vaccination during pregnancy would most likely provide temporary protection to vulnerable infants, for whom the burden of hospital admission and death remains the greatest (Saso and Kampmann 2016). GBS infection, perinatally acquired during birth may be prevented by vaccinating pregnant women and thereby eliciting high GBS-specific antibody levels. This, in turn, could potentially prevent perinatal transmission of GBS (i.e., transmitted from mother to newborn during birth). High antibody concentrations in the pregnant mother may also provide protection in infants against late onset of GBS disease by passively transferring these protective antibodies transplacentally (Baker, Carey et al. 2014, Rubin, Koso-Thomas et al. 2015). These infectious diseases, which are still highly prevalent in infants, are just a few examples of why maternal immunization efforts need to continue to be supported as a strategy to protect infants.

Maternal immunizations have been an effective strategy to protect both the mother and the infant against vaccine-preventable diseases. However, significant barriers remain that prevent the development and licensing of additional vaccines for maternal immunization strategies. Some of those barriers include ethics and policy considerations about including pregnant women in research, the need for continued support of pre-clinical and clinical research on immunity, the impact and safety of immunizations during pregnancy, and educating obstetrical providers about the benefits of immunizations during pregnancy and the importance of including pregnant women in clinical research to provide the highest quality of health care. The Department of Health and Human Services recognized

the need to address these barriers and subsequently charged the National Vaccine Advisory Committee with making recommendations that would address the problem.

Charge to the National Vaccine Advisory Committee

Recognizing the importance and impact of maternal immunizations on public health, the Assistant Secretary for Health (ASH) charged the National Vaccine Advisory Committee (NVAC) in June 2012 with reviewing the state of maternal immunizations and existing best practices to identify programmatic gaps and/or barriers to the implementation of current recommendations regarding maternal immunization. The NVAC established the Maternal Immunization Working Group (MIWG) in August 2012 to conduct these assessments and provide recommendations for overcoming any identified barriers. The NVAC separated the task into two sections as it was first necessary to address and understand the demand for maternal immunizations in order to then address the challenges in developing maternal immunizations.

The MIWG first focused on understanding the demand for maternal immunization programs by identifying existing patient and provider barriers to maternal immunization, and then shifted its focus to addressing the second part of the charge, which was to identify barriers to and opportunities for developing vaccines for pregnant women and to make recommendations to overcome these barriers. These two objectives were studied, considered, and recommendations issued separately, mainly because they necessitated different subject matter expertise. The first report recommended that the use of vaccines during pregnancy (such as those against influenza and pertussis disease) should be incorporated as a standard of obstetrical care as well as a standard of practice among any and all health care providers who administered health care services to pregnant women (National Vaccine Advisory 2015). The report that follows reflects the work of the second task group. Specifically, it lists the barriers and states the recommendations NVAC issued to address the second part of the charge, which was to identify barriers to and opportunities for developing vaccines for pregnant women and make recommendations to overcome these barriers. The NVAC working group initially identified four main focus areas on which to concentrate their efforts on. These included i) ethical issues; ii) policy issues; iii) pre-clinical and clinical research issues; and iv) provider education and support issues.

NVAC Recommendations and Conclusions

Focus Area 1: Ethical Issues

1.1 The Assistant Secretary for Health (ASH) should work with the Office of Human Research Subjects Protection (OHRP) and other relevant stakeholders and agencies to revise the current exclusionary climate of research in pregnancy. Such areas of focus include but are not limited to:

1.1.1 Institutional Review Board (IRB) guidance on interpretation of minimal risk

1.1.2 Code of Federal Regulations language surrounding research in pregnancy

1.1.3 Collaboration with bioethics experts, regulatory agencies, and the scientific community to optimize the design of studies to minimize the risk of interventions for research in pregnancy

1.1.4 Relevant regulations, statutes, and policies that should be modified to indicate that pregnant women are not a vulnerable population for the purposes of ethical review

1.2 The ASH should work with OHRP and the stakeholder community to develop policy and regulatory guidelines that would promote inclusion of pregnant women in clinical trials when scientifically appropriate

Exclusion of Pregnant Research Subjects. Participation in important areas of research continues to fall behind among women in general, and especially among the population of pregnant women, who are not frequently recruited to participate as vaccine research subjects. One could argue that the systematic exclusion of pregnant women from clinical research that might lead to significant benefits to the mother and the infant is harming, rather than protecting the woman and fetus from injuries, and that it is highly consequential. Although there is concern that including pregnant women in the study of new drugs and vaccines could potentially lead to fetal harm, it is critical to recognize that excluding pregnant women from research can also lead to harm. The most important historical example of this involved the use of

thalidomide during pregnancy (Committee on 2015). In this specific example, thalidomide had been approved in Europe and recommended for use during pregnancy, even though pregnant women had not been included in the clinical licensure studies. This widespread exposure could have been avoided had the drug been tested in pregnant women as well, which would have significantly reduced the number of affected children.

The majority of pregnant women are affected by illnesses that require treatment or immunizations during pregnancy, or require immunizations administered for the benefit of the infant. Nonetheless, very few drugs, and no immunizations, are currently approved or specifically indicated for use in pregnancy by the Food and Drug Administration (FDA). If the medical treatment of pregnant women is based on studies from which they were excluded as participants, a concern of generalizability must be raised, as pregnant women are at risk of not receiving the same level of care available to the rest of the population (Committee on 2015).

Another challenge that contributes to the exclusionary climate toward pregnant subjects in clinical trials is that currently researchers must justify for the regulatory authorities the inclusion of pregnant women and specify what special protections will be in place during the test of the product (Beigi, Fortner et al. 2014). Interestingly, there is no requirement to justify their exclusion from a protocol. In an effort to modify this approach, the wording of Subpart B of the Code of Federal Regulations (C.F.R.) (the human research subject protection rules that deal specifically with pregnant subjects) was changed in 2001 (45 C.F.R.§ 46 Subpart B). The new language states that pregnant women *may be* involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;(c) Any risk is the least possible for achieving the objectives of the research;(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when

risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;(g) For children as defined in § 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part; (h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and (j) Individuals engaged in the research will have no part in determining the viability of a neonate.(45 C.F.R. § 46.204).

Although this modification has relaxed the restrictions faced by Institutional Review Boards (IRBs) when evaluating protocols that propose the inclusion of pregnant women, it is still far from requiring a justification to exclude them from research. In the past, and in an attempt to address similar barriers, the Department of Health and Human Services (HHS) made successive modifications to the policies and statutes for inclusion of human research subjects, to eventually guarantee the inclusion of additional research subjects other than men (Public Law 108 – 155, Pediatric Research Equity Act of 2003) (Miller 2001, Weitz, Freund et al. 2001, Poon, Khanijow et al. 2013, Elahi, Eshera et al. 2016). These included women, ethnic minorities, and children, leaving pregnant women to be one of the only major populations for which justification for exclusion does not need to be given (45 C.F.R. § 46.112(a)(3)) (Blehar, Spong et al. 2013). These historical precedents highlight the fact that pregnant women are not the only population to have faced challenges for the ethical testing of drugs. In 1963, the pediatric population was deemed an accidental “pharmaceutical orphan” due to their systematic exclusion from clinical trials in order to avoid perceived safety and liability concerns (Statement of Harry C. Shirkey 1963, Rumore 2016). Several directives, such as the Pediatric Research Equity Act (Public Law 108–55, 2003), and the Best Pharmaceuticals for Children Act (Title V of Public Law 110-85; FDA Amendment Act

of 2007), were created in response to this claim, in order to deal with the discrimination against research on drugs that were being administered to children without including them in the pre-licensing testing. The result of these legislative efforts has been a marked increase in the number of clinical trials and studies that include pediatric subjects (Pasquali, Lam et al. 2012). A similar effort directed to require the inclusion of pregnant women in clinical trials might move the field towards a more balanced scientific consideration of issues.

Pregnant Women are Not a Vulnerable Population. One of the reasons that pregnant women have been systematically excluded from participating in clinical research, is that they are perceived as a vulnerable population. A vulnerable population is defined as one that has a compromised ability to protect its interests and provide informed consent (Blehar, Spong et al. 2013). However, pregnant women have the same decision-making capacity, ability to judge risks and benefits, and ability to provide informed consent as their non-pregnant counterparts. Thus, in 2010, a workshop sponsored by the National Institutes of Health (NIH) Office of Research on Women's Health, proposed that pregnant women in research trials should be defined as a "scientifically complex" rather than as a "vulnerable" population (Blehar, Spong et al. 2013, Committee on 2015). This classification is intended to reflect a combination of both physiological and ethical complexities that should be considered when balancing the interests of pregnant women and the newborn (Committee on 2015). This proposal was later supported by the American College of Obstetricians and Gynecologists (ACOG) expert committee opinion and the American Academy of Pediatrics (AAP) as well.

IRB Interpretation of Minimal Risk. Another barrier that directly influences the inclusion of pregnant women in the design of clinical research is the inconsistency of the interpretation of regulations across IRBs. IRBs are tasked with reviewing and approving research protocols ensuring the protection of the rights and welfare of human subjects. One of the most problematic issues that IRBs face is the interpretation of minimal risk. Without clear standards that define a threshold of acceptable risk associated with research, IRBs are left to strike a delicate balance between what they consider to be "acceptably-low" harm or discomfort, and the benefit accrued from conducting said research. This has been a serious point of concern that was raised by both federal and non-federal stakeholders, and that currently affects clinical research in other populations as well, but that is especially sensitive when reviewing research that calls for the protection of both the mother and the infant. Indeed in 2008, the

Secretary's Advisory Committee on Human Subjects Research (SACHRP) issued recommendations advising on the interpretation of minimal risk related to all subjects involved in clinical research, but did not address the population of pregnant women specifically (Tilden 2008). Although this advisory committee gave its view and expanded on the definition of minimal risk as stated in the C.F.R. (45 C.F.R. part 46), it also clearly pointed out that "[i]n its estimate of research-related risk, the IRB should carefully consider the characteristics of subjects to be enrolled in research including an evaluation of subject susceptibility, vulnerability, resilience, and experience in relation to the anticipated harms and discomforts of research involvement" (Tilden 2008). In view of this, there might still be a role for the government, informed by the SACHRP and other specialized committees, to contribute to the education of IRB members regarding specific requirements, ethical standards, and regulations for research for scientifically complex populations such as pregnant women. Clear and standardized definitions of minimal risk interventions for both the mother and infant would ensure that all IRBs have access to shared guidance in order to decide i) whether to include pregnant women in clinical research and ii) the quantity and quality of interventions that could be approved in the protocol in order to maximize the benefit of said research.

Finally, in addition to the active development of vaccines for pregnant women and prevention of infections in the newborn period, and similar to the 2009 H1N1 influenza pandemic, the current Zika virus outbreak has once again raised awareness about the need for developing and articulating a pregnancy-specific ethical framework that can offer guidance to IRB and investigators for clinical trials to promote the inclusion of pregnant women (Omer and Beigi 2016). This highlights that the need for manufacturers, researchers, IRBs, providers, and the public to understand the benefits of creating a culture of inclusion of pregnant women in clinical research is paramount.

Focus Area 2: Policy Issues

2.1 The ASH should continue to support maternal immunization as an important public health strategy to encourage manufacturer investment in the development of new and currently licensed vaccines for additional indications for use specifically in pregnant women

2.2 The ASH should advocate to the Secretary of Health and Human Services to resolve the uncertainties around coverage under the Vaccine Injury Compensation Program (VICP) for vaccines administered to pregnant women that are not recommended for use in children by the Centers for Disease Control (CDC), and for liability protections for live-born infants born to mothers vaccinated during pregnancy

Maternal Immunization as a Public Health Strategy. Despite remarkable strides as a global community in combating mortality in children under the age of five, the rate of infant deaths due to infectious diseases remains unacceptably high (UNICEF 2016, UNICEF 2016). Maternal immunizations have emerged as a promising global strategy to protect infants against vaccine-preventable infectious diseases (Lindsey, Kampmann et al. 2013, Amirthalingam, Andrews et al. 2014, Beigi, Fortner et al. 2014, Gerdts, van Drunen Littel-van den Hurk et al. 2016, Regan, de Klerk et al. 2016, Shakib, Korgenski et al. 2016). Two types of vaccines, seasonal inactivated influenza and Tdap, are already routinely recommended by CDC to be administered during pregnancy (Burney 1960, Harper, Fukuda et al. 2004, CDC 2011, CDC 2013), although there are currently no vaccines specifically indicated for use in pregnant women by the FDA. The lack of a specific indication for pregnancy for current vaccines, together with the fact that there are additional disease targets with significant morbidity and mortality affecting infants (Lindsey, Kampmann et al. 2013, Liu, Oza et al. 2015, Abramson and Mason 2016), motivates prioritizing the need for the development of new and improved vaccines for use by expectant mothers in order to successfully protect infants during the first months of life. Several immunizations that could be efficacious against infant disease are already being developed and include vaccines against RSV and GBS. The support of the public health community moving these prototypes through the pipeline is essential to ensure the success of the vaccines already in development and to promote the innovation of new vaccines that would address additional needs.

Liability Protection. Another significant hurdle preventing vaccine developers and manufacturers from fully committing to obtaining specific indications for use during pregnancy for new and developed vaccines is the uncertainty about the scope of coverage and liability protection for these vaccines under the Vaccine Injury Compensation Program (VICP) (42 U.S.C. § 300aa-10 to 300aa-15) (Health and Services Administration 2007). The VICP was created by the Childhood Vaccine Injury Act of 1986, as amended (Vaccine Act) (42 U.S.C. §§ 300aa-1 to 300aa-34), which also established the National Vaccine

Program Office (NVPO) and the Health Resources and Services Administration's (HRSA) Advisory Commission on Childhood Vaccines (ACCV), which makes recommendations to the Secretary on issues related to the operation and implementation of the VICP. The VICP provides compensation to people (regardless of age) found to have been injured by, or to have died as a result of, the administration of certain covered vaccines. Even in cases in which such a finding is not made, petitioners may receive compensation through a settlement. Compensation may be available for vaccine injuries sustained by adults or children so long as the general category of vaccines is covered by the VICP. In order for a vaccine to be covered by the VICP, the category of vaccine must be (1) recommended by the CDC for routine administration to children (adults immunized with these vaccines may also submit a claim to VICP) and (2) subject to an excise tax by Federal law.

The CDC currently recommends two immunizations for routine use among pregnant women: seasonal inactivated influenza and Tdap vaccines. These vaccines are covered under the VICP as they are also recommended for routine administration to children and are subject to an excise tax. Because these vaccines are covered under the VICP, the manufacturers and administrators of such vaccines generally are afforded the Vaccine Act's liability protections (Jacobs 2012). Although these two vaccines are currently covered under the provisions of the VICP, maternal immunizations in general still face several coverage gaps that endanger the current manufacturer's liability protection. Even as influenza and Tdap are covered under VICP, new categories of vaccines, that would potentially be only indicated for use during pregnancy and not routinely recommended for use in children, would not be covered under this program if they were not also recommended for use in children. Therefore, pregnant women receiving such vaccines would not be eligible to pursue claims related to such vaccines under the VICP. In order for such vaccines to be covered under current law (and absent a statutory amendment to cover other categories of vaccines), Congress would need to enact an excise tax with respect to such vaccines and the CDC would need to recommend this category of vaccines for routine administration to children (42 U.S.C. §§ 300aa-1 to 300aa-34).

Immunization Recipient. Even regarding vaccines currently covered under the VICP, a more detailed inspection of the Vaccine Act and VICP case law evidences another coverage gap with the potential to threaten liability protection. In the case of vaccines administered during pregnancy, uncertainty remains about whether a claim concerning an injury sustained *in utero* (after a pregnant woman's vaccination)

can be pursued under the VICP on behalf of the child. This is in part because petitioners claiming a vaccine-related injury to the VICP must demonstrate that the person who suffered a vaccine-related injury or death "*received a vaccine* set forth in the Vaccine Injury Table [a covered vaccine]" (42 U.S.C. § 300aa-11(c)(1)(A)). In claims alleging that a child suffered an injury *in utero* as a result of a vaccine administered to the pregnant mother, the question is whether the child received a vaccine under the meaning of the statute. The question of whether a vaccine is received *in utero* has been a central issue explored in few VICP cases involving allegations of injuries sustained *in utero* (Jacobs 2012). However, there is no binding case law resolving the issue, so it is one that remains unsettled.

The "*One Petition Rule*." The Vaccine Act also specifies that "[o]nly one petition may be filed with respect to each administration of a vaccine" (the "one petition rule") (42 U.S.C. § 300aa-11(b)(2)). To the extent that more than one VICP petition is filed with respect to a single vaccine administration, the second petition may be dismissed as barred by the Vaccine Act. In the event that two VICP petitions are filed with respect to a vaccine administration to a pregnant woman (i.e., one petition on behalf of an injured child *and* a separate petition on behalf of an injured mother), it would appear that the "one petition rule" would be violated. However, in this case, there is not a binding case law interpreting the provision either, so the issue is also unresolved.

Also administered by HRSA, the Countermeasures Injury Compensation Program (CICP) provides compensation for serious injuries and deaths directly caused by the administration or use of "covered countermeasures" identified by the Secretary in declarations issued under the Public Readiness and Emergency Preparedness (PREP) Act (42 U.S.C. § 247d-6d). The PREP Act provides the Secretary with authority to promulgate regulations to govern the procedures and requirements of the CICP. The regulation issued pursuant to that authority addresses the issue of injuries suffered by children born to women who were administered or used a covered countermeasure during pregnancy. The CICP's regulation specifies that a child can qualify as an "injured countermeasure recipient" for purposes of the Program if the child survives birth, and is born with, or later sustains, a covered injury as the direct result of the mother's administration or use of a "covered countermeasure" during pregnancy (42 C.F.R. 110.3(n)(3); 75 FR 63660).

Recognizing the effect that certain changes to the VICP could have on such an important public health objective as the protection of vulnerable infants, two of the HHS' Advisory Committees ACCV and NVAC have already recommended the coverage of claims submitted to the VICP alleging injuries to the pregnant woman and/or her live-born infant for injuries sustained *in utero*, resulting from maternal immunization (which also may result in liability protections for the vaccines' manufacturers and administrators). This recommendation has also been supported by relevant stakeholders such as AAP and ACOG, members of Congress (including authors of the original legislation that established the VICP), and representatives of the pharmaceutical industry (Jacobs 2012, Harkin 2015).

Unfortunately, uncertainties regarding maternal immunizations and liability protections under the VICP represent a barrier that discourages manufacturers and vaccine developers from i) investing in developing new vaccines for use in pregnancy and; ii) pursuing pregnancy-specific indications for vaccines already recommended by the CDC to be routinely administered to women during pregnancy. Modifications to the VICP program in order to resolve these uncertainties should be a priority to incentivize manufacturers to invest in safe and effective vaccinations specifically formulated for use during pregnancy.

Focus Area 3: Pre-Clinical and Clinical Research Issues

3.1 The ASH should prioritize increased support for pre-clinical and early clinical research to understand the immune response during pregnancy and to develop vaccines for pregnant women:

3.1.1 The ASH should work with federal and non-federal stakeholders to create or promote mechanisms that support investigator-initiated and other types of research that fosters innovation and expands the field of vaccines for pregnant women

3.2 The ASH should emphasize the need for a better understanding of the public health burden of diseases preventable by maternal immunization

3.3 The ASH should work with CDC, NIH, and other relevant federal agencies to support evaluation of the maternal and neonatal outcomes of vaccines administered during pregnancy

with respect to the (1) safety of vaccines and (2) effectiveness of vaccines to reduce maternal and infant morbidity and mortality caused by vaccine-preventable diseases, and (3) to better understand the potential risks and benefits of maternal immunization

3.4 The ASH should support continuing evaluation of vaccines in pregnant women and infants born to vaccinated mothers, while advocating for the adoption of standardized approaches to data collection, analysis, and safety evaluation

3.5 The ASH should support the adoption and utilization of standardized definitions of possible maternal and neonatal outcomes to evaluate the safety and effectiveness of vaccines administered during pregnancy

3.6 The ASH should convene stakeholders and other federal agencies to work on the expansion of pharmacovigilance systems that readily link maternal and infant electronic health records and safety surveillance systems

Pre-clinical and Clinical Research Barriers to Advancing Vaccine Development for Pregnant Women. Despite the scientific advances in understanding vaccines and human immune response to vaccines, there is still rather limited knowledge on maternal-fetal physiology and immunology, especially the immunological role of the placenta and the potential effects that maternal immunizations can have on the fetus, which remain poorly understood. A better understanding of topics such as: immunologic responses in women during pregnancy; antibody transfer from mother to fetus (transplacental transfer); antibody kinetics (the rate at which maternal antibodies are transferred to the fetus and the half-life of maternal antibodies, especially after transfer to the fetus); the optimal period for greater maternal immunization in relation to the period of disease and infectivity risk; the rate of antibody waning in the infant and its correlation with protection against infection or other outcomes of disease, and whether maternal antibodies persist during infancy; the potential effect of maternal antibodies on the infant's responses to primary immunization; and the role of breast milk antibodies, is still needed in order to fully understand the benefits and risks of maternal immunizations (Beigi, Fortner et al. 2014). The knowledge gap in the maternal immunization immunology field is partially due to the lack of available funding mechanisms to address these questions. Expanding federal funding to allow for investigator-

initiated or exploratory research is a way to increase the studies that would address some of the areas mentioned above. Alternative pathways of funding would also promote research flexibility to explore the unknowns about the biology and immunology of maternal immunization and advance the maternal immunization field.

Furthermore, additional information on the safety and effectiveness of vaccines recommended for use during pregnancy could also improve implementation of maternal immunizations recommendations and, consequently, vaccination rates. The currently recommended maternal vaccines (influenza and Tdap) are not specifically indicated by FDA for use in pregnant women since pre-licensure trials did not include testing the safety and efficacy of the vaccine in the pregnant women population. The limited data available on pregnant women are usually obtained from non-randomized or observational clinical trials, which often exclude pregnant women from participating (Beigi, Fortner et al. 2014). Observational studies or retrospective studies present a problem since they are not designed to understand specific aspects of vaccine physiology, such as the effects and benefits of vaccines when administered in early pregnancy (first and second trimesters). Because of this lack in pre-licensure testing by the vaccine sponsor and the potential public health importance of maternal immunization against influenza and pertussis, ACIP/CDC gathered enough additional research data to support the wisdom of immunization recommendations for pregnant women, even though the vaccine sponsor had not sought a specific indication for use in pregnancy (Burney 1960, Harper, Fukuda et al. 2004, CDC 2011, CDC 2013). However, the inconsistency between federal recommendations and specific indications leads obstetric providers to be unsure about making strong recommendations for maternal vaccinations as there is a limited understanding of the immunogenicity and safety of vaccine delivery during pregnancy (Omer and Beigi 2016). Finally, the exclusion of pregnant women from pre-licensure clinical trials has also influenced the availability of safety information, as vaccine safety data on maternal immunizations has been mostly obtained from retrospective population-based cohort studies and database reviews, which are not the ideal study design to determine the safety profile of a vaccine prior to or following licensure (Beigi, Fortner et al. 2014).

Understanding Disease Burden in Order to Better Inform Maternal Immunization Programs. A more thorough understanding of vaccine-preventable disease burden that affects infants in the first six months of life would also help with the accurate determination of the effectiveness of maternal

immunizations on both the infant and the mother, and can help justify the importance of this intervention to policymakers and the general public as they prioritize health resources. Systems capable of tracking epidemiological data and disease burden for poorly surveyed diseases in both the United States and globally, would enhance evidence-based decision making for the recommendation and administration of vaccines during pregnancy, and support increased funding for research into maternal vaccine development. It is worth mentioning that two national efforts are already implementing some of the additional features needed to estimate disease burden. The National Notifiable Diseases Surveillance System (NNDSS, managed by the CDC) incorporated a new initiative called the NNDSS Modernization initiative (NMI), which has the main goal of "modernizing the systems and processes used to receive nationally notifiable disease data to provide more comprehensive, timely, and higher quality data than ever before for public health decision making" (CDC 2016). NMI is an effort to strengthen and modernize the infrastructure supporting CDC's system for notifiable disease as part of their existing surveillance system already in place and , but also to improve the system further to allow a more comprehensive, timely, and higher quality data for public health decisions (CDC 2016). The Department of Defense (DoD) also employs the Global Emerging Infections Surveillance and Response System (DoD-GEIS), which focuses on surveying emerging infectious diseases that could affect the United States military (Russell, Rubenstein et al. 2011), often used to make informed public health decisions (Parms 2016). Systems already in place could be used as infrastructure to collect disease burden data including and focusing on specific populations, such as pregnant women and infants, which are needed to better assess the justification and needs for vaccine development (Higgins, Trujillo et al. 2016, PATH 2016, PATH 2016).

Enhancing Safety Surveillance for Maternal Immunizations. Vaccine safety surveillance and research on pregnant women and their infants present unique challenges compared to immunization safety research conducted in other populations. Well established post-marketing vaccine adverse events reporting and surveillance systems allow for the study of vaccines currently in use, and to research diverse safety outcomes, even in the absence of reports of a specific adverse event. Implementing new or adapting existing surveillance systems can help facilitate maternal immunization research studies to improve the understanding of vaccine safety and immunogenicity in pregnant women and their infants, and can help identify very rare outcomes potentially associated to vaccine administration such as some types of congenital anomalies.

In the United States, the increased availability of nationwide electronic health records (EHs) and interconnected state-based immunization information systems (IIS) are potentially underutilized and invaluable resources to study the effects of vaccination in pregnant women and also follow their infants. There are currently two pharmacovigilance systems in place that employ EHRs to assess the safety of immunizations: the Vaccine Safety Datalink (VSD) managed by CDC (Davis, Black et al. 1997, Baggs, Gee et al. 2011, McNeil, Gee et al. 2014) and the Post-licensure Rapid Immunization Safety Monitoring (PRISM) system managed by FDA (Nguyen, Ball et al. 2012, Baker, Nguyen et al. 2013). These safety systems systematically analyze and link immunization registry and electronic health outcome data from several large integrated health plans to conduct near real time vaccine safety surveillance for pre-specified outcomes and targeted studies using automated data. Any potential safety signals identified from these automated studies can be further refined by accessing individual EHRs to validate cases. Adapting VSD and PRISM to surveying and assessing maternal immunizations safety outcomes has been somewhat challenging because it requires the modification of analytical algorithms to address hurdles such as the direct linking of the maternal and the infant clinical records. These existing surveillance systems utilize such prototype algorithms which could be further modified, expanded, and improved to allow for additional capabilities in areas such as direct mother and infant record-linking, and to enhance studies of very rare birth outcomes (e.g., some types of congenital anomalies).

Standardization of Data Collection, Analysis, Safety Evaluation, and Outcomes Definitions. To advance maternal immunization studies, it is important to recognize that clinical trials need to be conducted in a systematic manner in order to fully benefit from the results obtained. Several considerations make research including pregnant women uniquely challenging: IRBs lack proper guidance when approving protocols for research during pregnancy, pregnant women are notoriously harder to recruit for clinical trials, some clinical endpoints might be rare or difficult to define, and risks for safety outcomes that are usually found with extremely low prevalence in other populations, are harder to estimate given the background rate of common pregnancy complications (Omer and Beigi 2016). These considerations emphasize the need for standardized collection of data, analysis, and safety surveillance not only in the United States but globally in order to correlate results and issue findings that have been reproduced in multiple settings.

One of the critical aspects of reproducible data collection for surveying of maternal and infant safety outcomes, is the standardization of vaccine safety terminology and common case definitions, which may have surprisingly varied interpretations among obstetric and pediatrics practitioners. Standardizing vaccine obstetric, fetal, and neonatal safety terminology and case definitions would enable not only the United States, but other countries around the globe, to combine clinical study results when investigating vaccines during pregnancy, and to obtain significant risk determinations even for very rare maternal and infant birth outcomes. The Brighton Collaboration, a non-profit, scientifically independent global research network consisting mainly of volunteers, is one of the leaders in this effort, with the mission of advancing the science of immunization safety and defining globally acceptable common terminology for adverse events following immunization (Kohl, Bonhoeffer et al. 2005, Kohl, Gidudu et al. 2007, Munoz, Eckert et al. 2015). The World Health Organization (WHO), along with the Brighton Collaboration, share the objective of (1) raising awareness of the availability of standardized case definitions and guidelines for data collection, analysis and presentation for global use, and (2) developing and implementing standard study protocols for evaluating case definitions (WHO 2016). In collaboration, they provide independent, high-level, technical, and strategic advice focused on developing an interim set of key terms and concept definitions for the assessment of safety of vaccines given during pregnancy in the mother and the infant, which can be used to improve vaccine safety monitoring and evaluation. Obtaining a standardized definition that could be implemented globally is a complex process that requires thoroughness. The process involves recruiting international working groups who conduct systematic literature reviews to develop the case definitions; the definitions are then revised by a reference group, and then finalized to be distributed for global use (Bonhoeffer, Kohl et al. 2002). Examples of standardized safety outcomes definitions include ‘Stillbirth’ and ‘Congenital Abnormalities’ among others, which were recently released in order to aid collaborative immunization safety research studies (Collaboration 2016, Da Silva, Gonik et al. 2016, DeSilva, Munoz et al. 2016). Supporting these efforts will ensure that we are on the right path towards effective and reproducible surveillance of the safety of immunizations administered during pregnancy.

Focus Area 4: Provider Education and Support Issues

4.1 The ASH should encourage professional societies to continue to support the inclusion of pregnant women in clinical research

4.2 The ASH should work with relevant stakeholders to increase awareness among obstetric providers and pregnant women about the importance of vaccine research during pregnancy

4.3 The ASH should work with professional societies to educate obstetricians and other obstetric providers on vaccination and interpretation of new regulations regarding labelling (i.e., the Pregnancy and Lactation Labeling Rule) so they can make informed decisions and counsel their patients more effectively

Support from Professional Societies. Maternal immunizations are an investment in better health outcomes for both pregnant women and their infants (Beigi, Fortner et al. 2014). Professional societies and maternal immunization stakeholders have a critical role in educating providers about the benefits of involving pregnant women in clinical research. Their community engagement efforts are essential to supporting a shift of the paradigm towards including pregnant women in order for the mother and infant to benefit from safe and effective vaccines that have been appropriately tested during the pre-licensure phase of clinical research. This will ensure that pregnant women have access to the same standard of care that other members of society have been afforded. However, even when the policy, regulatory, and ethical barriers to licensing safe and effective immunizations for use in pregnancy are addressed, pregnant women's recruitment and participation in research trials are the cornerstones for developing any vaccine with a specific indication for use during pregnancy. Pregnant women may be reluctant to enroll in clinical research due to a general lack of awareness about research in their community, which could lead them to express unease and distrust of the research (Frew, Saint-Victor et al. 2014). Pregnant women's hesitancy to participate could be altered by consulting with obstetrical providers, who are the most trusted advisors for a pregnant patient, and thus uniquely positioned to advocate for increased participation of pregnant women in clinical research (CDC 2012, Ding, Black et al. 2015). This is when the work of professional societies and other relevant stakeholders to influence healthcare professionals becomes invaluable, since the former have the ability to conduct outreach efforts to community providers, educate them, and encourage them to promote research studies to their patients. In many cases, a clinician's promotion of research will in turn increase a pregnant

woman's willingness to participate in studies (ACOG 2016). Increases in maternal immunization rates for influenza and Tdap have recently occurred following efforts by federal agencies and professional societies as detailed above.

The Pregnancy and Lactation Labeling Rule. Professional societies that have an interest in advocating for the safe use of medications and vaccines during pregnancy also should facilitate clinicians' transition into understanding of new and unique immunization product information. For example, professional societies should help clinicians understand FDA's new Pregnancy and Lactation Labeling Rule, also called PLLR (21 C.F.R 201.57 and 201.80; 79 FR 72963). In short, a critical step in the FDA's review process of a Biologics License Application (BLA) includes the evaluation of the product package insert (Roberts and Gruber 2015). Until recently, the FDA required that biologics' labels (for biologics, including vaccines), contained a letter code summarizing the determination of a risk category in for the biologic's letter coding (A, B, C, D, or X) for use in during pregnancy (A, B, C, D, or X). This was required for any biologic, including vaccines, without a specific indication for use during pregnancy (sometimes erroneously referred as "off-label" use), and was intended to provide the practitioner with a classification of the product according to the level of risk for pregnant women and infants, depending on the data available to the sponsor at the time of licensing. However, this system was difficult to interpret in practice, and cumbersome to convey to the patient when explaining the risk-benefit balance of administering a medication during pregnancy. In response to these challenges, the FDA recently amended the letter category rules with the PLLR (21 C.F.R. 201.57 and 201.80; 79 FR 72963). The PLLR eliminates the old classification and provides a new framework to describe more clearly the available data on the potential risks associated with use of drugs and biologics during pregnancy and lactation. This change not only allows for a consistent format for communicating risk and benefit information of a vaccine relevant to pregnant and lactating women, but it also enables the incorporation of exposure information from a variety of sources, including non-industry-sponsored epidemiological and interventional studies (Omer and Beigi 2016). As with any new regulation, the implementation of the rule will have challenges. Obstetric and other health care providers, who are unfamiliar with the new classification, will require guidance on how to best interpret the new package inserts. A clear understanding by both clinicians and patients of the labeling of vaccines administered during pregnancy will also promote confidence in the safety and efficacy of these products, which may lead to a more active participation of this population in clinical research during pregnancy.

Conclusion

Maternal immunization has been implemented as a successful national and global strategy to protect infants against vaccine-preventable diseases such as influenza, pertussis, and tetanus. Although CDC already recommends the use of vaccines during pregnancy, certain ethical, policy, education and research barriers remain to be addressed in order to improve uptake of currently recommended vaccines and promote the development of additional maternal immunizations. This NVAC report describes the barriers and opportunities for developing vaccines for pregnant women and makes recommendations to overcome those barriers. The NVAC submits these recommendations to the ASH for her consideration.

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