Pregnancy in the Time of Zika
Addressing Barriers for Developing Vaccines and Other Measures for Pregnant Women

Three recent infectious disease outbreaks of global importance—H1N1 influenza, Ebola, and now Zika—have had specific implications for pregnant women. For the H1N1 pandemic, pregnant women and their infants were high-risk groups for severe complications and death. During the Ebola outbreak, there were concerns about worse outcomes among pregnant women and specific concerns regarding vertical transmission of infection to newborns. The current Zika outbreak, with its ostensible association with microcephaly, has direct and highly concerning implications for pregnant women and women of reproductive age.

Yet the global public health community again lacks the optimal tools for dealing with a disease that has specific and important implications for pregnant women. There are substantial knowledge gaps in current understanding of Zika, irrespective of the affected population. However, Zika’s association with adverse fetal outcomes requires that pregnant women be a priority group for developing and evaluating vaccines and other measures. There are several current scientific and structural barriers to developing vaccines for pregnant women. These barriers challenge the ability to prepare and respond to epidemics and are particularly highlighted during a public health emergency that has pregnant women and their unborn fetuses as the primary affected population.

One barrier is a lack of a broadly accepted ethical framework for guiding clinical research during pregnancy. For example, the term minimal risk—a concept that informs ethical review of research—is not well defined for research in pregnancy. Therefore, institutional review boards (IRBs) often resort to categorizing most intervention research in pregnancy as high risk, often without a balanced consideration of the risks of not performing the research. Moreover, the risks and benefits to the fetus also need to be considered along with risks and benefits to the mother, adding to the challenge. This lack of a broadly accepted ethical framework has a chilling effect on both academic and industry-led clinical research in pregnancy. Therefore, there is a need for development and articulation of a pregnancy-specific ethical framework that can offer guidance to investigators and IRBs.

Pregnancy is a physiologically dynamic state. The immune profile of a pregnant woman is responsive to the changing levels of sex hormones and evolves through the course of pregnancy. However, most of the current knowledge base for vaccine response is derived from observational studies conducted in the latter part of pregnancy, with limited data available from the first and early second trimester or from randomized clinical trials. On the other hand, clinical, practical, and public health considerations require that vaccine use not be restricted to women with advanced gestational age. Given that a substantial portion of Zika’s teratogenic effects may occur in the earlier phase of pregnancy, administration of any forthcoming Zika vaccine will be most beneficial prior to or during the early parts of pregnancy. The knowledge gap for early pregnancy vaccine responses and safety will make the task of developing and recommending an effective Zika vaccine for use across pregnancy challenging.

Until recently, the pregnancy and lactation sections of US Food and Drug Administration (FDA)-approved labels for vaccines and pharmaceuticals contained ambiguous information with limited clinical utility. For example, the labels were required to contain determination of letter risk categories (A, B, C, D, or X) for pregnancy. These categories were an attempt to summarize convey risk of reproductive and developmental adverse effects. However, the categories were somewhat simplistic and challenging to translate into practice in a clinically meaningful manner.

After years of deliberations, revisions, and public comment, FDA recently issued the Pregnancy and Lactation Labeling Rule (PLLRR). This rule will enable inclusion of clinically relevant and interpretable information in drug and vaccine labels and creates a consistent format for communicating information on risks as well as benefits relevant to pregnant and lactating women and for males and females of reproductive potential. Moreover, the new rule allows for incorporating information about risk and benefits from a variety of sources, including non–industry-sponsored epidemiological and interventional studies. Although the release of the PLLRR is important and holds promise to provide more clinically useful information, its implementation faces many logistical challenges. For example, there is a need for a “mock label” (ie, a sample label providing examples of information to be included in the sections relevant to pregnancy and lactation) to provide guidance for inclusion and...
format of pregnancy-related information in sections relevant to pregnant women.

General understanding of the new categorization system is insufficient among clinicians who provide obstetrical care. Therefore, it will take concerted efforts to phase in this categorization. Having clarity regarding vaccine (and drug) labeling related to pregnancy will help ensure that clinicians have a higher level of confidence in pregnancy-related vaccines and could provide a road map for conducting research that can inform labeling and hence clinical decisions.

Robust safety evaluation is a cornerstone of any vaccine development and deployment program. There has been an increase in the number of studies evaluating the safety of currently recommended maternal vaccines, such as influenza and pertussis vaccines. Despite increased attention on the evaluation of safety of immunization in pregnancy, barriers remain. For example, a review commissioned by the World Health Organization highlighted the lack of standard definitions of outcomes, and standards for measurement of these outcomes, relevant to evaluation of vaccines in pregnancy. This lack of standardization poses a challenge for conduct of clinical trials, generalizability of safety data, and merging of large safety data sets. This last point is critical because large multi-location data sets could optimize the evaluation of rare but clinically important outcomes, such as microcephaly.

Moreover, safety assessment for pharmaceutical interventions against emerging public health threats requires real-time assessment of these outcomes, relevant to evaluation of vaccines in pregnancy. This lack of standardization poses a challenge for conduct of clinical trials, generalizability of safety data, and merging of large safety data sets. This last point is critical because large multi-location data sets could optimize the evaluation of rare but clinically important outcomes, such as microcephaly.

Having clarity regarding vaccine (and drug) labeling related to pregnancy is important for promoting safe use.Baseline outcome rates are an essential input for such an assessment. The value of baseline rates was recognized during the H1N1 pandemic. Since then, there has been little progress in ascertaining baseline rates in different geographic locations of outcomes such as first trimester miscarriages. Ascertainment of baseline rates of outcomes is even more important when a disease emerges in the context of other infections (eg, malaria) that are associated with adverse birth outcomes.

Drug and vaccine development and evaluation in children may provide some context for the current outbreak response. Pediatricians and child health researchers recognized many parallel challenges in the amount and quality of data available for the care of children. The term therapeutic orphans was coined for children, stressing the concept of the lack of information available to prevent and treat disease in children. To address these challenges, efforts were mobilized around the conceptualization and passing of legislation (Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act). These efforts have contributed to improving the quantity and quality of research that has been conducted in children. A similar approach may also be relevant to fostering research in pregnancy.

Pregnant women have been a high-risk group requiring special consideration for several recent global public health emergencies. Currently, pregnant women and their unborn children are the focal point of the Zika outbreak. Although there are several barriers for developing vaccines and other measures for pregnant women, these barriers are surmountable with concerted efforts and leadership. Strategic planning and action have allowed for advances in pediatric drug development and provide a good model. However, the time to act is now, before the next epidemic takes its toll.

ARTICLE INFORMATION


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REFERENCES


