

Pregnant Women & the Zika Virus Vaccine Research Agenda: Ethics Guidance on Priorities, Inclusion, and Evidence Generation

Provides ethics guidance and recommendations for the inclusion of pregnant women in Zika virus vaccine research and development.

Updated last **September 20, 2017**
for the 06/29/2017 report.

WHAT IT DOES

The [Wellcome Trust](#), a global charitable foundation, funded the formation of the [Ethics Working Group of ZIKV Research & Pregnancy](#) to analyze the ways in which pregnant women can be fairly and ethically included in Zika virus (ZIKV) vaccine research and development. This group formed in response to the recent rapid spread of ZIKV; their recognition of the general exclusion of pregnant women from vaccine research and development, including for ZIKV; and their acknowledgement that pregnant women at risk of contracting ZIKV have a particular interest in protecting the health of themselves and their offspring through mechanisms such as vaccines.

The working group developed a report entitled [Pregnant Women & the Zika Virus Vaccine Research Agenda: Ethics Guidance on Priorities, Inclusion, and Evidence Generation](#), which is intended for various stakeholders in ZIKV vaccine research and development. These stakeholders include health organizations, policymakers, vaccine developers, researchers, health providers, patients, and human trials participants, among others.

The report first asserts three ethical imperatives of Zika virus vaccine research as they pertain to pregnant women:

1. "The global research and public health community should prioritize development of ZIKV vaccines that will be acceptable for use by pregnant women in the context of an outbreak;
2. "The development of all ZIKV vaccines targeted to women of childbearing potential, whether expected to be acceptable for use in pregnancy or not, should include timely collection of data to inform judgments about safety and efficacy of administration in pregnancy;" and
3. "Pregnant women at risk of ZIKV infection should have fair access to participating in ZIKV vaccine trials that carry the prospect of direct benefit."

More broadly, the authors outline four ethical principles in regards to pregnant women's participation in biomedical research:

1. "Pregnant women deserve an evidence base for the prevention and treatment of their illnesses equal to others as a matter of justice;
2. "Pregnant women should not be categorized as a 'vulnerable population' for purposes of human subjects research review;
3. "It is ethically permissible to conduct research with pregnant women that meets specific risk standards;" and
4. "Justice requires that pregnant women have fair access to research that offers the prospect of direct benefit."

The working group utilized these imperatives and ethical principles to develop fifteen recommendations regarding how relevant actors can safely and ethically include pregnant women and their interests in various stages of ZIKV vaccine research and development:

1. "Pregnant women should be affirmed as a priority population for ZIKV vaccines intended for use in areas experiencing ongoing transmission and in future outbreaks;
2. "Financial and other in-kind resources should be allocated to fund and facilitate development of ZIKV vaccines that will be

- acceptable for use in pregnancy;”
3. Incentives should be identified and utilized to encourage the development of ZIKV vaccines that will be acceptable for use during pregnancy;
 4. Data should be collected regarding outcomes of safety and efficacy of vaccine administration during pregnancy;
 5. “Prospective studies should be conducted with pregnant women who receive the vaccine in public health and clinical settings to systematically collect data from them and their offspring;”
 6. Data should be collected regarding outcomes of safety and efficacy of administration during pregnancy from instances in which trial participants are unknowingly pregnant or become pregnant within a relevant window of time;
 7. In the case that a vaccine is inadvertently administered to a pregnant woman, systematic collections and analyses of safety and efficacy data from them and their offspring should be carried out;
 8. At least one expert in maternal health and one expert in pediatrics should be involved in vaccine research and development activities;
 9. “The perspectives of pregnant women should be taken into account in designing and implementing ZIKV vaccine trials in which pregnant women are enrolled or in which women enrolled may become pregnant;”
 10. “Data on background rates of adverse pregnancy and birth outcomes should be regularly collected and analyzed for populations that will receive ZIKV vaccines;”
 11. “All findings on ZIKV vaccine use in pregnancy should be communicated with sufficient contextual information and adequate translation... to ensure that the evidence is appropriately interpreted and communicated;”
 12. “Pregnant women should be eligible for prospective enrollment in ZIKV vaccine trials that offer a prospect of direct benefit unless it can reasonably be judged that the risks of participation outweigh the potential benefits;
 13. “Women participating in ZIKV vaccine trials who become aware of a pregnancy during the trial should be guaranteed the opportunity, through a robust re-consent process, to remain in the trial;”
 14. “Women participating in ZIKV vaccine trials who become aware of a pregnancy should [in all circumstances] receive all study-related ancillary benefits associated with trial participation;” and
 15. “When a pregnant woman of a legal age to consent is judged eligible to participate or continue in a ZIKV vaccine trial, her consent alone is sufficient to authorize her participation.”

RELEVANT SCIENCE

[Zika virus](#) is an emerging disease caused by a [Flavivirus](#). The virus is predominantly transmitted through the bite of the [Aedes egypti mosquito](#), which inhabits much of the southern United States, as well as tropical and subtropical areas in Central America, the Caribbean, South America, Africa, the Pacific Islands, and Asia. The virus can also be [transmitted](#) through vaginal, anal, and oral sexual activity; through blood transfusions; and from mother to fetus during pregnancy. Infected persons can infect others even when they are not symptomatic, and it is unknown how long ZIKV can survive in a host.

Zika virus often does not present [symptoms](#) in adults who are affected, but the 20% of infected persons who do become symptomatic most often experience fever, rash, headache, joint pain, pinkeye, and/or muscle pain. [According to the US Centers for Disease Control and Prevention](#) (CDC), there have been over 41,000 symptomatic cases reported in the United States since 2015.

Although adult symptoms of ZIKV are relatively mild, ZIKV can be extremely harmful to a developing fetus if a pregnant woman is exposed. Zika virus exposure can result in fetal death, [microcephaly](#), and other abnormalities that are collectively known as [Congenital Zika Syndrome](#). The report notes that congenital Zika syndrome presents difficulties for both the mother, who often faces emotional distress and stigma while dedicating time and resources to caring for her affected infant, and the child, who often requires continuous medical care and may not gain full functional abilities.

Although nearly [40 vaccine candidates](#) are currently under development, there is currently no approved medication or vaccine available for ZIKV treatment or prevention. However, experts believe that the [wide range of categories](#) of ZIKV vaccine candidates—[namely](#), whole inactivated viral vaccines, subunit vaccines, nucleic acid vaccines, live attenuated virus vaccines, and viral-vectored vaccines—and the previously safe and efficacious use of some of these vaccine types in other vaccinations for pregnant women means that a ZIKV vaccine could be created that would be safe for pregnant women to receive.

If developed and approved, experts think a vaccination given to pregnant women will likely prevent both maternal ZIKV infection and in utero exposure to the fetus, [as do other vaccinations](#) administered during pregnancy. Because of the dual protection offered by most vaccines, the CDC now [recommends](#) many vaccinations for pregnant women, and the CDC's [Advisory Committee on Immunization Practices](#) states that the benefits of vaccinating pregnant women usually outweigh the potential risks.

WHY IT MATTERS

The report presents a comprehensive document of ethics guidance for pregnant women's participation in ZIKV vaccine research and development to be used by current and future stakeholders, especially given the context that pregnant women have historically not been involved in such research. In doing so, it also develops ethics recommendations which can be more broadly applied to the inclusion of pregnant women in biomedical research and vaccine development.

This report was particularly pertinent recently as a major epidemic of ZIKV occurred from 2015 to 2016, in which ZIKV rapidly [spread](#) from Brazil to other parts of South America and North America. The lack of existing preventative medicine and medical treatment for the disease [spurred](#) a large-scale scientific response to developing a vaccine. More [recently](#), ZIKV incidence has decreased, but experts warn that the virus may return to epidemic proportions in the future. This report outlines recommendations that are imperative for vaccine research and development so that public health efforts may be better prepared for future outbreaks.

RELEVANT EXPERTS

[Dr. Anne Drapkin Lyerly, MD, MA](#) is a professor of social medicine at the University of North Carolina School of Medicine and the Assistant Director of the Center for Bioethics at the University of North Carolina, Chapel Hill. Her research focuses upon morally and socially complex issues within women's health and reproductive health. She also co-founded the Obstetrics and Gynecology Risk Research Group and the [Second Wave Initiative](#). Dr. Lyerly served as the co-principal investigator of the report detailed here.

"People tend to think first about the ethical problems of including pregnant women in research. In this case, the gravest ethical problem would be if we failed to include them, since it is pregnant women – and their babies – who will face the most serious consequences of infection."

Relevant Publications:

- Lyerly, Anne Drapkin, Samantha G. Robin, and Elena Jaffe. 2017. "Rubella and Zika Vaccine Research—A Cautionary Tale about Caution." *JAMA Pediatrics* 171(8): 719–720. doi: [10.1001/jamapediatrics.2017.1496](#)
- Lyerly, Anne Drapkin, Margaret Olivia Little, and Ruth Faden. 2008. "The Second Wave: Toward Responsible Inclusion of Pregnant Women in Research." *International Journal of Feminist Approaches to Bioethics* 1(2): 5–22. doi:[10.1353%2Fijf.0.0047](#)

ENDORSEMENTS & OPPOSITION

At present, there has not been any publicly reported endorsement or opposition to this report.

Regarding the broader issue of including pregnant women in clinical research trials, the following endorsements have been made:

- [Dr. Kristine E. Shields](#) and [Dr. Anne Drapkin Lyerly](#) stated in their 2013 *Obstetrics & Gynecology* [article](#): "We found the exclusion of pregnant women from industry-sponsored clinical trials to be common practice. Moving beyond reflexive exclusion and developing thoughtful criteria for inclusion of pregnant women in clinical research would likely advance the evidence base to inform treatment decisions during pregnancy and lead to better health outcomes for women and children."
- A team of physicians and researchers from the US Food and Drug Administration and the National Institutes of Health stated in a 2013 *Women's Health Issues* [article](#), "There is a clear and compelling rationale for increased pregnancy research in order to

address the pressing therapeutic needs of pregnant women. Additionally, there is accumulating evidence that pregnancy provides a unique window into understanding fundamental mechanisms underlying observed links between a pregnant woman's health and her later health and the health of her children. While pregnancy research raises myriad complex issues and challenges, its clinical value and its potential for generating new scientific knowledge about lifespan and intergenerational development demand that the challenges be met.”

- [Dr. Ruth Macklin](#) stated in an [article](#) in the *International Journal of Feminist Approaches to Bioethics*, “Although no one questions the importance of preventing pregnant women, their fetuses, and their future children from avoidable harms that could be caused by experimental drugs, several reasons can justify the inclusion of pregnant women in a greater number of biomedical studies than current practice allows. The most compelling reason is the need for evidence gathered under rigorous scientific conditions, in which fewer women and their fetuses would be placed at risk than the much larger number who are exposed to medications once they come to market.”

Regarding the inclusion of pregnant women in vaccine research, the following opposition has been made:

- [Dr. Matthew Memoli](#), director of the clinical studies unit in the Laboratory of Infectious Diseases at the National Institutes of Allergy and Infectious Diseases, stated in an [interview](#): “We always have to test these [vaccines] in a healthy population before we put pregnant mothers and their fetuses at risk.”

STATUS

The document was published in June 2017.

ORGANIZATIONS

The [Ethics Working Group on ZIKV Research & Pregnancy](#) is funded by [Wellcome Trust](#). The working group is made up of 15 experts in medicine, public health, philosophy, vaccine research, and bioethics; additional experts were also consulted. Most members are medical doctors and/or university professors; individual group members' affiliations are available in the [report](#).

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RECOMMENDED CITATION

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