EXECUTIVE SUMMARY

Pregnant Women & the Zika Virus Vaccine Research Agenda:

Ethics Guidance on Priorities, Inclusion, and Evidence Generation

Ethics Working Group on ZIKV Research & Pregnancy

June 2017

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Introduction

The rapid spread of the Zika virus (ZIKV) has galvanized the global public health community toward development of ZIKV vaccines. The most dire consequence of ZIKV infection, congenital Zika syndrome (CZS), is a result of infection during pregnancy. As a consequence, pregnant women figure prominently in global concerns about ZIKV. They should also figure prominently in ZIKV vaccine development, but the way forward is not well established.

Historically, the needs of pregnant women have not been adequately represented in the development of biomedical interventions, including vaccines. New products are rarely designed with the specific needs of pregnant women in mind, and for many interventions evidence about safety and efficacy in pregnancy is limited and late in coming. Investigators have also been reticent to conduct interventional biomedical research with pregnant women. There are many causes for this reticence, including misinterpretations or overly cautious interpretations of what is allowed under research regulations and international norms, as well as concerns about legal liability. Moreover, biomedical research with pregnant women is ethically complicated. Assessments of risk and prospect for benefit must take into account the interests of both the pregnant woman and the fetus, which are usually but not always aligned.

In the case of ZIKV, the interests of pregnant women and their offspring do align. Pregnant women have the deepest interest in the health of their babies, and will suffer along with their children if CZS is not averted. Nevertheless, significant questions remain about what specifically is required to ensure that these interests are adequately protected and fairly taken into account in ZIKV vaccine research and development (R&D). Guidance is also needed on the conditions under which is it ethically acceptable, if not required, to include pregnant women in ZIKV vaccine trials. These questions are of particular urgency as the pace of vaccine development accelerates and threats to pregnant women and their offspring from new outbreaks continue.

The Ethics Working Group on ZIKV Research & Pregnancy

To address these questions, we received funding from the Wellcome Trust to form the Ethics Working Group on ZIKV Research & Pregnancy. Our fifteen-member Working Group is comprised of experts in bioethics, public health, philosophy, pediatrics, obstetrics and maternal–fetal medicine, vaccine research, and maternal immunization, including five colleagues from Latin America.

To ensure that our recommendations were grounded in the most up-to-date state of the science and public health response to ZIKV, we conducted consultations with over 60 leading experts in vaccine science and immunology, flaviviruses and general virology, clinical trial design, public health and emergency preparedness, obstetrics and maternal–fetal medicine, pediatrics, infectious diseases, research ethics, and legislative and regulatory affairs concerning vaccines and biologics. These consultations were supplemented with extensive reviews of the scientific literature and academic research on international ethics guidance and regulations regarding research with pregnant women, and historical analyses exploring concepts of risk perception.

Our guidance applies to the current situation of continuing ZIKV outbreaks with limited effective prevention modalities and no existing vaccine approved for use, as well as to any future scenarios in which critical evidence gaps remain on the safety and efficacy of ZIKV vaccines in pregnancy. We focus on research and development efforts for ZIKV vaccines intended for use in the context of ZIKV outbreaks. This focus coheres with that of the Target Product Profile of the World Health Organization (WHO) to coordinate research efforts and set priorities for ZIKV vaccine development. Furthermore, ZIKV vaccines meant for use in the context of an outbreak are the ones that will be most needed for use in pregnancy to prevent the imminent risks of congenital ZIKV exposure.

The guidance outlines three moral imperatives: (1) to develop a ZIKV vaccine that can be responsibly and effectively used during pregnancy, (2) to collect data specific to safety and immunogenicity in pregnancy for all ZIKV vaccine candidates to which pregnant women may be exposed, and (3) to ensure pregnant women have fair access to participate in ZIKV vaccine trials that offer a reasonably favorable ratio of research-related risks to potential benefits. From these imperatives, the guidance specifies concrete recommendations for how a range of relevant actors can ensure ethical inclusion of pregnant women's interests at various stages in ZIKV vaccine research and development and across the product lifecycle.

RECOMMENDATIONS

IMPERATIVE I

The global research and public health community should pursue and prioritize development of ZIKV vaccines that will be acceptable for use by pregnant women in the context of an outbreak.

Significant efforts are currently underway to develop ZIKV vaccines with the primary objective of preventing congenital Zika syndrome (CZS). Not every ZIKV vaccine candidate under development needs to be acceptable or suitable for use in pregnancy.

However, the strategy of developing a vaccine targeted to women of childbearing potential (WOCBP) before they become pregnant, while critically important, will not be sufficient to effectively and equitably prevent the harms of CZS. Previous experience with immunization programs underscores that not all women will be immunized ahead of pregnancy, leaving them and their offspring unprotected from CZS. Moreover, evidence demonstrating that the risks associated with congenital ZIKV infection persist into the second and third trimesters negates concerns that a ZIKV vaccine would only offer benefit if administered early in or ahead of pregnancy.

By **acceptable for use in pregnancy** we mean that relevant advisory bodies, public health practitioners, and policymakers could support the use of such a vaccine by pregnant women in an outbreak setting based on the expected benefits associated with the vaccine and its safety profile.

Recommendation 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.

- **DIRECTED TO** relevant global and national health organizations, policymakers, funders, and other entities who are shaping the ZIKV vaccine research agenda.

Recommendation 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.

- **DIRECTED TO** relevant global and national health organizations, policymakers, sponsors, funders, and research institutions in a position to contribute resources, financial or otherwise.

Recommendation 3. Available and appropriate incentive mechanisms should be identified and leveraged to support development of ZIKV vaccines that will be acceptable for use pregnancy. Strategies to mitigate disincentives that would impede such development should be pursued.

- **DIRECTED TO** relevant policymakers, regulatory authorities, vaccine advisory committees, sponsors, and funders that oversee and/or administer programs that create incentives or mitigate disincentives that may influence product development decisions and strategies.

IMPERATIVE II

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.

Two important sets of considerations stand behind this imperative:

[1] *Failure to gather appropriate and timely data about vaccine use in pregnancy can significantly delay or deny pregnant women and their offspring the potential benefits of safe and effective vaccines, and*

[2] *Inadequate data on vaccines to which pregnant may be inadvertently exposed can lead to unnecessary harms in the event of unintentional administration. Without appropriate data, public health officials, providers, and pregnant women will be unable to make informed decisions about the responsible use of ZIKV vaccines in pregnancy and the responsible management of unintentional exposures to ZIKV vaccines in pregnancy.*

For ZIKV vaccine candidates under development that are anticipated to be acceptable for use in pregnancy in public health programs and clinical settings:

Recommendation 4. Clinical development plans should include timely collection of data on key indicators and outcomes of safety and efficacy of administration in pregnancy, including data collected from a cohort of pregnant study participants (and their offspring) who are enrolled in clinical trials at the same time as other general population study groups.

- **DIRECTED TO** vaccine developers, sponsors, oversight bodies, and regulatory authorities.

For all authorized ZIKV vaccines deemed acceptable for use in pregnancy:

Recommendation 5. To further develop the evidence base on the safety and efficacy of administering these vaccines in pregnancy, 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.

- **DIRECTED TO** public health agencies, manufacturers, and researchers. Where applicable, regulatory authorities should utilize available, enforceable mechanisms to require post-authorization research and pharmacovigilance plans for pregnant women and their offspring.

For ZIKV vaccine candidates under development that are not anticipated to be acceptable for use in pregnancy but are targeted to women of childbearing potential:

Recommendation 6. Clinical development plans should include systematic collection of relevant indicators and outcomes of safety and efficacy of administration in pregnancy from all instances in which women participating in trials are unknowingly pregnant at the time of exposure or become pregnant within a relevant window of vaccine administration.

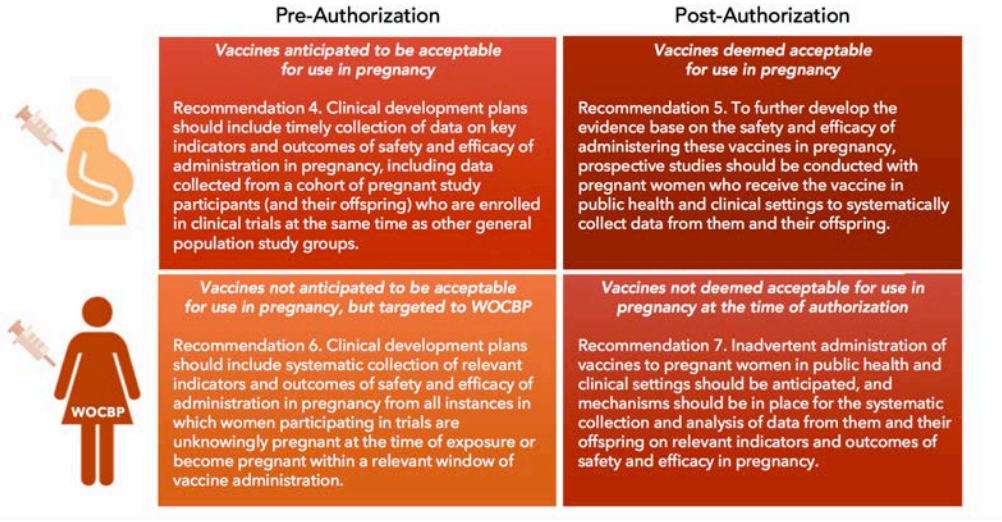
- **DIRECTED TO** vaccine developers, sponsors, oversight bodies, and regulatory authorities.

For ZIKV vaccines authorized for use in public health programs, outbreak responses, or other non-research contexts that are not deemed acceptable for use in pregnancy at the time of authorization:

Recommendation 7. Inadvertent administration of vaccines to pregnant women in public health and clinical settings should be anticipated, and mechanisms should be in place for the systematic collection and analysis of data from them and their offspring on relevant indicators and outcomes of safety and efficacy in pregnancy.

- **DIRECTED TO** public health agencies, manufacturers, and researchers. Where applicable, regulatory authorities should utilize available, enforceable mechanisms to require such systems and post-authorization study.

FIGURE ES.1 | SUMMARY OF RECOMMENDATIONS 4–7



**WOCBP: Women of childbearing potential*

Recommendation 8. At least one expert in maternal health and one expert in pediatrics should be involved in activities responsible for the design, ethics oversight, generation, analysis, and evaluation of evidence on ZIKV vaccines, including activities involving vaccines trials and observational studies, research ethics review, data and safety monitoring, regulatory review, and public health registries and surveillance.

- **DIRECTED TO** researchers, research ethics committees, data and safety monitoring boards, data analysts, oversight bodies, regulatory authorities, and public health agencies.

Recommendation 9. Whenever possible, 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 in order to increase the likelihood that trial design will best advance the interests of pregnant women.

- **DIRECTED TO** research ethics committees and those developing and implementing vaccine trial protocols and observational studies.

Recommendation 10. Data on background rates of adverse pregnancy and birth outcomes should be regularly collected and analyzed for populations that will receive ZIKV vaccines. These data are necessary to appropriately interpret and communicate to the public, and especially to pregnant women, whether any findings of adverse outcomes following ZIKV vaccine administration during pregnancy are appropriately attributable to the vaccine.

- **DIRECTED TO** funders, public health agencies (especially those overseeing routine health information systems), researchers, and maternal and child health providers.

Recommendation 11. All findings on ZIKV vaccine use in pregnancy should be communicated with sufficient contextual information and adequate translation of their significance for health policy, clinical practice, and personal decision-making to ensure that the evidence is appropriately interpreted and communicated.

- **DIRECTED TO** those responsible for communicating with policymakers, clinicians, patients, trial participants and study communities, and the media.

IMPERATIVE III

Pregnant women at risk of ZIKV infection should have fair access to participating in ZIKV vaccine trials that carry the prospect of direct benefit.

Denying pregnant women fair access to participate in ZIKV vaccine trials conducted in areas of active local transmission will unjustly exclude these women and their offspring from the prospect of direct benefit they may realize from receiving an investigational vaccine.

Fair access requires that eligibility to enroll or continue in a trial depend on reasonable assessments of the potential benefits of participation in relation to research-related risks for the woman and her future offspring. Fair access also requires that pregnant women are permitted to authorize or decline participation on their own.

Recommendation 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.

- **DIRECTED TO** those developing and implementing vaccine trial protocols, regulatory authorities, research ethics committees, and other entities that have oversight over human subjects research.

Recommendation 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 and complete the vaccine schedule when the prospect of direct benefit from completing the schedule can reasonably be judged to outweigh the incremental risks of receiving subsequent doses.

- **DIRECTED TO** those developing and implementing vaccine trial protocols, regulatory authorities, research ethics committees, and other entities that have oversight over human subjects research.

Reasonable judgments of a favorable balance of research-related risks and benefits entail credible interpretation of available evidence that the probability and magnitude of research-related risk is outweighed by the probability and magnitude of prospective benefit.

Recommendation 14. Women participating in ZIKV vaccine trials who become aware of a pregnancy should receive all study-related ancillary benefits associated with trial participation to which they would otherwise be entitled even if they withdraw from or are ineligible to continue receiving (remaining) vaccine doses; these women should be offered the remaining doses postpartum, where appropriate.

- **DIRECTED TO** those developing and implementing vaccine trial protocols, regulatory authorities, research ethics committees, and other entities that have oversight over human subjects research.

Recommendation 15. When a pregnant woman of 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.

- **DIRECTED TO** those developing and implementing vaccine trial protocols, regulatory authorities, research ethics committees, and other entities that have oversight over human subjects research.

The Way Forward

ZIKV vaccines are expected to be a critical weapon in the arsenal against near-term and future ZIKV outbreaks. Adequately addressing the specific interests of pregnant women in ZIKV vaccine R&D efforts is not only essential to mitigating the potential harms faced by pregnant women and their offspring, it is also a matter of justice and respect. This guidance provides concrete recommendations to ensure the needs of pregnant women and their offspring are adequately and ethically addressed in the public health response to ZIKV with regard to vaccine R&D. Although a complex challenge, through concerted and proactive efforts to address the needs of pregnant women and their offspring early and across the ZIKV vaccine R&D pathway, we can ensure that pregnant women are responsibly and equitably included in ZIKV vaccine research and development efforts and that, as a consequence, pregnant women and their offspring will benefit from the global investment in ZIKV vaccines.