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Ethics, pregnancy, and ZIKV vaccine research & development

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1. 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 ZIKV Syndrome (CZS), results from 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, often many

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Conflict of interest

Allison August is currently an employee of Valera Tx, a Moderna Venture. Just prior to Valera, she was employed by Novavax, Inc.

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years after licensure [1]. 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 [2,3]. 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 the interests of pregnant women and their offspring are adequately protected and fairly taken into account in ZIKV vaccine research. Guidance is also needed on the conditions under which is it ethically acceptable, if not required, to include pregnant women in ZIKV 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 [4].

2. The Ethics Working Group on ZIKV Research & Pregnancy

To address these questions, the Wellcome Trust provided funding to form the Ethics Working Group on ZIKV Research & Pregnancy. The Working Group is comprised of 15 experts in bioethics, public health, philosophy, pediatrics, obstetrics, maternal-fetal medicine, vaccine research, and maternal immunization, including 5 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, maternal-fetal medicine, obstetrics, pediatrics, 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 by a historical look at rubella vaccine policy in pregnancy.

3. The guidance

Our guidance applies to the current situation in which the threat of ZIKV outbreaks is on-going, effective prevention modalities are limited, and no vaccine is approved for use. It also applies to any future scenarios in which important evidence gaps remain on the safety and efficacy of ZIKV vaccines in pregnancy. In line with the WHO's Target Product Profile (TPP) for ZIKV vaccine development, we focus on research and development efforts for ZIKV vaccines intended for use in the context of ZIKV outbreaks [5]. It is during ZIKV outbreaks that vaccines will be most needed for use in pregnancy to mitigate imminent risks of congenital ZIKV exposure.

We identified three overarching imperatives to ensure the ethical inclusion of pregnant women in the ZIKV vaccine research agenda, which are summarized below. The full guidance report expands upon these imperatives and provides 15 specific recommendations to actualize them [6].

3.1. Imperative I. The global research and public health community should pursue and prioritize development of ZIKV vaccines that will be acceptable for use in pregnancy in the context of an outbreak

Significant efforts are currently underway to develop ZIKV vaccines with the primary objective of preventing CZS [4]. Not every ZIKV vaccine candidate under development needs to be acceptable or suitable for use in pregnancy. However, we believe it is essential that the ZIKV research and development (R&D) community work collaboratively and expeditiously to develop vaccines that will be acceptable for use in pregnancy in the context of an outbreak.

In the initial efforts to coordinate R&D activities in response to ZIKV threats, the WHO Target Product Profile (TPP) called for development of vaccines targeted to women of childbearing age [5]. The strategy of developing a vaccine targeted to women of childbearing potential 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 [7]. Moreover, we now know that the risks of ZIKV-related harms persist throughout pregnancy and that immunization could offer significant benefits beyond the first trimester. In light of this evidence, the WHO updated their TPP for ZIKV vaccines for an outbreak response to more explicitly include pregnant women [5]. This signaled an important shift in thinking among global experts on the importance of addressing the needs of pregnant women in the ZIKV vaccine response.

We commend this shift and call for pregnant women to be widely affirmed as a priority population for ZIKV vaccines intended for use in areas experiencing ongoing transmission and in future outbreaks. Financial and other in-kind resources need to be allocated to finance and facilitate development of ZIKV vaccines appropriate for use in pregnancy, and incentive mechanisms should be aligned and leveraged to promote development of such vaccines.

3.2. 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. First, for vaccine candidates that are anticipated to be acceptable for use in pregnancy, the experience of other immunization programs suggests that gaps and delays in generating evidence about use in pregnancy can result in significant numbers of avertable deaths and disability. The failure to gather data while vaccine candidates are still under investigation can negatively affect vaccine acceptance and adoption by public health officials, clinicians and pregnant women,

resulting in unnecessary delays in, if not outright denials of, access to the benefits of safe and effective vaccines by pregnant women and their offspring [8].

Second, because women of childbearing potential will be a primary target population for ZIKV vaccine programs, it is inevitable that sizeable numbers of pregnant women will be inadvertently administered vaccines deemed not acceptable for use in pregnancy. Thus, even for vaccine candidates not anticipated to be acceptable for pregnancy, data about vaccine use in pregnancy are critically important. The price of ignorance about the implications of unintended exposure is significant and includes tremendous anxiety about impact on offspring, unnecessary pregnancy terminations, and confusion about whether offspring will be protected against ZIKV in this or in subsequent pregnancies.

Fig. 1 summarizes our recommendations for different categories of vaccines during product development and post-authorization. For ZIKV vaccine candidates anticipated to be acceptable for use in pregnancy, we emphasize the importance of enrolling a cohort of pregnant study participants at the same time as other general population study groups are enrolled in order to collect data on key indicators of safety and efficacy in them and in their offspring. These data, while critically important, will need to be augmented after vaccines are approved for general use to further develop the evidence base for the safety and efficacy of administering the vaccines in pregnancy. It is not too soon to be thinking about the design and resourcing of prospective studies with pregnant women who will be administered ZIKV vaccines in public health and clinical settings, and their offspring.

For vaccine candidates that are not anticipated to be acceptable for use in pregnancy, it is critical that protocols and resources be in place in anticipation that, as happened in other vaccine trials, women participating in trials will be unintentionally administered the vaccine during or shortly before pregnancy. Data collected from these women and their offspring, as well as other kinds of data collected pre-clinically, could be of great importance, as could data collected when these vaccines are inadvertently administered to pregnant women once the vaccines are being used in clinical and public health settings [9]. Again, it is not too soon to be scrutinizing and improving existing systems for capturing such data, and developing new systems, as appropriate.

We also emphasize the importance of having reliable data on background rates of adverse pregnancy and birth outcomes for populations that will receive ZIKV vaccine. We call for the collection of such data where it does not currently exist, particularly where trials are likely to be conducted and ZIKV outbreaks are most likely to occur. Without reliable information on background rates, it will be difficult to appropriately interpret and communicate to the public whether any reports of adverse outcomes following ZIKV vaccine administration during pregnancy are appropriately attributable to the vaccine [10].

3.3. 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

The principle of fair access to research involving the prospect of direct benefit to participants is a key and independent pillar of research ethics [11]. The greater the potential benefits at stake in participation, the more important it is not to exclude a class of persons who are

otherwise eligible for inclusion. Pregnant women are no exception to this principle. Indeed, in the case of ZIKV vaccine trials and many other research contexts, if benefits materialize, they accrue to two individuals, not just one: the woman herself, as well as the future offspring she carries. Denying pregnant women fair access to participate in ZIKV vaccine trials unfairly excludes them and their offspring from the prospect of direct benefit they may realize from receiving an investigational vaccine.

In the case of research with pregnant women, 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 offspring. Those involved in assessing risks and benefits and making determinations about eligibility criteria should avoid historical tendencies to distort and inflate fetal risk as they carefully consider the available evidence. They should also consider the risks to pregnant women and their offspring from *not* participating in vaccine trials, that is, the risk of the disease and its sequelae.

Unless it can be reasonably judged that the risks of participating in a particular ZIKV vaccine trial outweigh the prospect of benefit associated with protecting pregnant women and their offspring from the risk of harm from ZIKV and CZS, pregnant women should be considered eligible to enroll in ZIKV vaccine efficacy trials. This same standard should be applied when considering whether women who become pregnant during a multi-dose ZIKV vaccine trial should be offered the opportunity to receive subsequent doses. When the benefits of receiving additional doses of vaccine can be reasonably judged to outweigh the risks of doing so, pregnant women should be guaranteed the chance to complete the vaccine schedule, through a robust re-consent process.

Fair access also requires that when pregnant women of legal age to consent are judged eligible to participate in or continue to receive a vaccine schedule in a ZIKV trial, it is critical that their consent, and their consent alone, is sufficient to authorize or decline participation. While researchers should support pregnant women who wish to involve partners, family members, and other personal supports in their decisions, decision-making authority about participation must ultimately reside with the women themselves.[1]

4. The way forward

ZIKV vaccines are expected to be a critical weapon in the arsenal against near-term and future Zika outbreaks. Adequately addressing the specific interests of pregnant women in ZIKV vaccine research and development efforts is essential to mitigating the potential harms faced by pregnant women and their offspring. It is also a matter of fairness and respect. Our report provides three guiding imperatives and 15 concrete recommendations to help ensure that the needs of pregnant women and their offspring are adequately and ethically addressed in the vaccine component of the public health response to Zika.

[1]We recognize that significant numbers of women become pregnant below the legal age of consent for research participation within their countries. In some contexts, the state of being pregnant may provide pregnant girls the legal option to authorize consent on their own. Whether a pregnant girl is legally permitted to authorize research participation on her own will vary by jurisdiction. Whether and when a young pregnant woman should be allowed to independently consent to research participation - without authorization from a parent or legal guardian - is a complex issue that is beyond the scope of this guidance.

Implementing these recommendations will require the collective efforts of a wide range of actors who are positioned to influence ZIKV vaccine research activities and outputs, including global and national policymakers, regulatory authorities, funders and sponsors, vaccine manufacturers, research institutions, individual researchers, and oversight bodies. Although a complex challenge, through concerted and proactive efforts, pregnant women and their offspring will benefit fairly from the global investment in ZIKV vaccines, and the tragedy that is CZS will be maximally averted.

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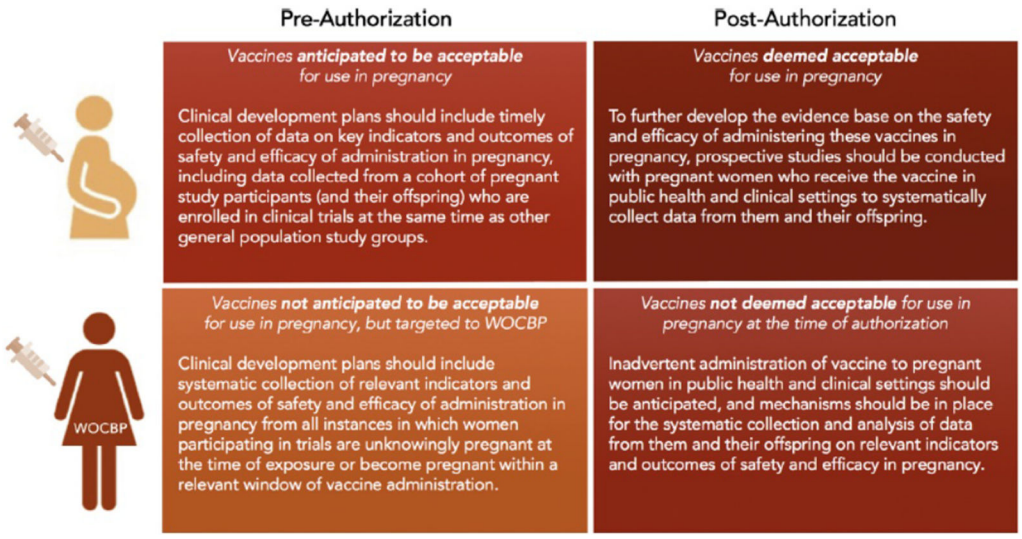

Fig. 1.

Generating appropriate, adequate and timely evidence for ZIKV vaccines, pre- and post-authorization.