

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

Ethics Working Group
on ZIKV Research
& Pregnancy

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EXECUTIVE SUMMARY

Pregnant Women & the Zika Virus Vaccine Research Agenda:

Ethics Guidance on Priorities, Inclusion, and Evidence Generation

EXECUTIVE SUMMARY

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 it is 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

	Pre-Authorization	Post-Authorization
	<p><i>Vaccines anticipated to be acceptable for use in pregnancy</i></p> <p>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.</p>	<p><i>Vaccines deemed acceptable for use in pregnancy</i></p> <p>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.</p>
	<p><i>Vaccines not anticipated to be acceptable for use in pregnancy, but targeted to WOCBP</i></p> <p>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.</p>	<p><i>Vaccines not deemed acceptable for use in pregnancy at the time of authorization</i></p> <p>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.</p>

*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.



Pregnant Women & the Zika Virus Vaccine Research Agenda:

**Ethics Guidance
on Priorities,
Inclusion, and
Evidence Generation**

INTRODUCTION

The rapid spread of the Zika virus (ZIKV) and its devastating consequences for normal fetal development have galvanized the global public health community toward development of ZIKV vaccines. Because the most dire consequences of ZIKV result from infection during pregnancy, challenging questions have arisen about how, when, and in what ways vaccine research and development (R&D) should address the specific interests of pregnant women and their offspring.¹ Although challenges raised by the intersection of pregnancy and biomedical research are not limited to ZIKV vaccine development, there are added layers of complexity given the centrality of pregnancy to the crisis, the outbreak context with its various emergency response mechanisms, the limited and evolving knowledge base of the virus and its pathophysiology, the lack of good alternative modes of prevention, and the rapid pace of the ZIKV vaccine research.

To address these questions and challenges, we received funding from the Wellcome Trust to form the Ethics Working Group on ZIKV Research & Pregnancy.² Our fifteen-member Working Group is comprised of experts in bioethics, public health, philosophy, pediatrics, obstetrics, maternal–fetal medicine, vaccine research, and maternal immunization, and includes five colleagues from Latin America. Our task was to develop concrete ethics guidance for including the needs and interests of pregnant women in the ZIKV vaccine research agenda.

To ensure that our guidance was grounded in the most up-to-date state of the science and public health response to ZIKV, our team 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, 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 policy in pregnancy. Further information about the members of the Working Group and our methodological approach can be found in **Appendices A-C**.

¹ We use the term “women” throughout this document because, while we appreciate that individuals who don't identify as women can still become pregnant, transgender and gender non-conforming individuals face different (though also substantial and problematic) barriers to participating in clinical research that lie beyond the scope of this paper.

² This charge to develop guidance for the inclusion of pregnant women's interests in ZIKV research falls under a two-year project with a goal of developing a broad framework for the responsible and ethical inclusion of pregnant women in biomedical research responding to a range of emerging infectious diseases and public health emergencies.

Our guidance is organized around three overarching imperatives to ensure the ethical inclusion of the interests of pregnant women in the ZIKV vaccine research agenda and across the product life cycle: (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 balance of potential benefits to research-related risks. These imperatives are actualized in 15 specific recommendations directed at a range of actors including global and national policymakers, regional and national regulatory authorities, funders and sponsors, vaccine manufacturers, research institutions, trial networks and research groups, individual researchers, oversight bodies, ethics review committees, and community advisory boards.

The guidance applies to the current situation where the threat of ZIKV outbreaks is ongoing, 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. It is in ZIKV outbreaks that vaccines for use in pregnancy will be most needed. When the risk of ZIKV infection is low and routine immunization efforts are ongoing, vaccine administration might reasonably be delayed until the postpartum period. However, in the context of an outbreak, when there is imminent risk of infection, access to vaccines to protect pregnant women and their offspring is critical and urgent.

To situate our guidance, we begin by summarizing background information on the virus and the ZIKV vaccine research pipeline, as well as the historical context surrounding the intersection of pregnancy, biomedical research, and the public health response to outbreaks of emerging and re-emerging infectious diseases.

BACKGROUND

Zika Virus and Congenital Zika Syndrome: The Need for a Vaccine

The Zika virus (ZIKV) is a single-stranded RNA flavivirus, closely related to dengue, Japanese encephalitis, West Nile virus, and yellow fever (1). ZIKV infection in adults tends to be mild and self-limiting, but ZIKV infection in pregnancy can be devastating to a developing fetus. In utero ZIKV exposure can lead to a wide number of adverse consequences, including pregnancy loss and multiple abnormalities including severe microcephaly, ocular malformations, congenital joint contractures, seizure disorders, and other serious birth defects that are collectively referred to as congenital Zika syndrome (CZS) (2–5). We now know that exposure to ZIKV poses substantial risks to normal fetal development not only in the first trimester, but in the second and third trimesters as well (2,6). Among infants born with CZS, the type and severity of conditions vary significantly and evidence is still accumulating on the range of adverse sequelae attributable to congenital ZIKV infection (7,8). Significant questions remain on potential longer-term effects of congenital ZIKV infection, including what neurological and musculoskeletal effects and developmental delays may emerge as babies with in utero exposures advance through infancy and childhood (9).

The dire consequences of CZS extend not only to affected children but also to their families and broader communities (10). Women who give birth to infants with CZS suffer along with their children. They experience significant and on-going emotional and psychological distress, and often bear much if not most of the burden of caring for their children's intensive needs. Most infants born with CZS require continual medical attention and therapy, and many will never gain critical functional abilities. In addition to the time and resources mothers and families dedicate to caring for their affected infants, they must also navigate applications for government support, which in many cases is sparse and difficult to obtain, while managing to support other children and family members (11). Additionally, many mothers of children with CZS face social stigma and abandonment from partners and communities (12,13). Though the most critical challenge in these situations will be to improve the health and well-being of affected children, the toll that ZIKV will take on mothers, families, and communities cannot be overstated.

These devastating consequences of CZS underscore the need for an efficacious vaccine to prevent the serious harms of ZIKV infection. Because ZIKV is both mosquito-borne and sexually transmitted, vector control efforts alone are not sufficient. Moreover, pregnant women may face greater exposures than others in the population to both these sources of infection (14–16). While the frequency and magnitude of future large-scale outbreaks are

hard to predict, there is growing consensus that, following acute outbreaks in areas with local transmission, there will be sustained endemicity that may cause isolated cases and localized outbreaks for years (17). Additionally, with global travel patterns, alerts remain high that ZIKV could be introduced or re-introduced in areas with competent mosquito vectors to sustain new outbreaks and epidemics (18). As a consequence, ZIKV will sustain the specter of fear and uncertainty for any pregnant women living in or traveling to areas where ZIKV may be circulating, highlighting the importance of continuing to work toward development of an efficacious vaccine, even as threat levels wax and wane in different geographic regions. (See Appendix D for more detailed information about the virus, its history, modes of transmission, clinical manifestations, and epidemiological trends.)

The State of Vaccine Development

Though a comprehensive response to ZIKV will require a combination of prevention efforts, it is widely agreed that vaccines will be a critical piece of the overall strategy. To this end, ZIKV vaccine development is occurring at an unprecedented speed. There are approximately 40 ZIKV vaccine candidates under development. Many of these are still in the preclinical stages of development, but a few are already advancing into Phase I and II clinical trials (19–21).

Although some candidates under development are better suited to longer-term strategies for routine childhood or adolescent immunization, most of the efforts are focusing on vaccines that can be deployed in the context of an outbreak. This focus on ZIKV vaccines for use in outbreaks reflects the priorities of the WHO, as detailed in the TPP document (22). The TPP specifies the primary target populations and desired characteristics (e.g., platforms, adjuvants, dosing schedule) of ZIKV vaccines intended for use in outbreaks (19,22). As we noted above, outbreak contexts are precisely where and when pregnant women without pre-existing immunity to ZIKV will most need a vaccine to prevent CZS.

ZIKV vaccine candidates employ a range of vaccine platforms, summarized in Box 1. Different platform technologies can influence the suitability of a vaccine candidate for use in an outbreak, as well as its suitability for use in pregnancy. For instance, some platforms may require multiple doses over a longer period of time to produce sufficient immunological protection and would be less desirable than vaccines that can be administered in a single dose. At the same time, vaccines that require only one dose to produce immunity often employ platforms that are replication-competent, and thus tend to be contraindicated in pregnancy.

NON-REPLICATION-COMPETENT VACCINE PLATFORMS

1. Whole inactivated viral vaccines. Inactivated or killed vaccines are often the preferred product platform for pregnant women because they do not pose even a theoretical risk of infecting the woman or fetus with live viral components. Often these vaccines require adjuvants to boost the immune response, and some adjuvants have a track record of use in pregnancy (e.g., alum). On the other hand, because inactivated vaccines tend to be less immunogenic than live attenuated products, they often require multiple doses, which is not ideal in an emergency or outbreak situation.

2. Subunit vaccines. Subunit vaccines contain fragments (subunits) of the pathogens they protect against, which subsequently provoke a protective immune response. Like killed vaccine platforms, subunit vaccines cannot cause infection. However, the vaccine must contain the specific antigenic proteins to elicit an adequate and durable (long-lasting) immune response, which can be difficult to identify. These vaccines also often require multiple doses and/or adjuvants.

3. Novel nucleic acid vaccines (mRNA/DNA). These vaccines inject a portion of the virus's DNA or mRNA into the body to produce an immune response. The body's cells then construct proteins that look like the virus, causing the immune system to produce antibodies. The associated risks in pregnancy are not well characterized, in part because no DNA or mRNA vaccine has yet been approved for use in humans. However, nucleic acid vaccines, like inactivated and subunit platforms, present no possibility of infection of the fetus with the virus. Although generally found to be well-tolerated, these candidates have not been as immunogenic as other vaccine platforms in humans to date. There is the potential advantage of rapid development and production, and indeed the first ZIKV vaccine candidates to enter clinical development utilized DNA and mRNA-based constructs. Rollout of these platforms may require new delivery systems or training on novel routes of administration.

REPLICATION-COMPETENT VACCINE PLATFORMS

4. Live attenuated virus vaccines. These vaccines use a weakened form of the pathogen to induce an immune response. They often require only a single dose to produce long-lasting immunity. However, live attenuated vaccines are typically not used in pregnancy because of the theoretical risk that a weakened but replication-competent virus could cross the placenta to infect the fetus and produce adverse pregnancy and birth outcomes. But, live yellow fever vaccines have been given to pregnant women in situations

of increased risk of exposure and pregnant women have been inadvertently vaccinated with different live attenuated vaccines, including the rubella vaccine. These exposures have produced no evidence of increased adverse pregnancy outcomes from immunization with currently licensed live-attenuated vaccines. Live attenuated ZIKV vaccines may raise particular concerns because the wild-type virus is itself a teratogen, alongside additional general safety concerns of ZIKV-associated GBS associated with vaccine administration.

5. Viral-vectored vaccines. Vectored vaccines use a weakened live virus to deliver DNA of the pathogen to the body to elicit an immune response. Although a vectored vaccine would not contain replicating Zika virus, there may be other concerns associated with the viral backbone (the “vector” virus used to deliver ZIKV DNA) and the tendency of some vectored vaccines to be associated with more severe vaccine-associated side effects.

Pregnant Women, Vaccines, & the Biomedical Research Agenda

Any analysis of ZIKV vaccine development and the needs and interests of pregnant women must take account of the complex and rapidly evolving approach to maternal immunizations, the dangers of delaying accrual of an evidence base for biomedical interventions during pregnancy, and emerging consensus on ethical principles governing research with pregnant women.

Maternal Immunizations

Maternal immunization can offer significant benefits in a variety of ways (23,24). Some vaccines primarily serve to protect the pregnant woman from serious morbidity or mortality. This includes cases where pregnant women are one among many at-risk populations facing exposure to a virulent pathogen (e.g., yellow fever), as well as cases where they face higher morbidity and mortality than other population groups (e.g., influenza) (25–27). In both instances, offspring also benefit. Preventing disease in a pregnant woman protects the fetus from harms of maternal illness and in utero exposures. Other maternal immunizations are aimed at preventing disease (e.g., pertussis) in newborns who are too young to receive vaccinations directly. Vaccinating pregnant women leads to conferred or passive immunity where maternal antibodies induced by the vaccine pass to the fetus. ZIKV vaccines will occupy a middle ground. Their primary purpose is to protect the next generation, but the target population is not exclusively pregnant women, and the vaccines will offer direct benefits to adults, such as protection against virus-related risks of Guillain-Barré Syndrome (GBS).

Despite the important role that maternal immunizations can play in preventing disease, there has historically been resistance to vaccinating women during pregnancy. Past public vaccination programs have tried to get around administering vaccines in pregnancy by focusing efforts on adolescents and children who are not yet of reproductive age or by interrupting viral circulation among young children to reduce exposure of pregnant woman, as in the case of rubella. Yet another strategy, called “cocooning,” (26,28), focuses on immunizing non-pregnant adults within the household. There is accumulating evidence, however, that these strategies often fail to adequately protect pregnant women and their offspring (29). Paradoxically, efforts to protect them from risks of vaccination have had the unintended consequence of exposing pregnant women and their offspring to greater risks from infection and illness. (30,31).

The critical importance of maternal immunizations is now increasingly recognized. In recent years, several vaccines developed for use by the general adult population have been endorsed for use in pregnancy. Multiple professional bodies recommend vaccination with inactivated influenza and tetanus, diphtheria, acellular pertussis (Tdap) for all pregnant women (32–34). The WHO now recommends the use of the yellow fever vaccine during pregnancy in outbreak contexts, even though it is a live attenuated vaccine with precautions issued for use in pregnancy (27). Other vaccines have been endorsed in pregnancy when there is a threat of exposure (e.g., hepatitis A and B, meningococcus, Japanese encephalitis) or as a post-exposure prophylaxis (e.g., anthrax, rabies, smallpox) (25).

There has also been a push to develop vaccines specifically targeted to pregnant women. This new vanguard of vaccines is aimed primarily at preventing illness in the newborn through conferred immunity from the mother. Research and development efforts are targeting pathogens to which infants are highly vulnerable and that are prevalent among newborns, such as respiratory syncytial virus (RSV) and group B streptococcus (23,35). Because pregnant women are the only targets for these vaccines, the pathways to development and licensure necessarily include research with pregnant women and require the generation of evidence specific to their use in pregnancy (25,36).

The Evidence Gap for Pregnant Women

Most preventives and treatments developed for the general population lack evidence to guide decisions about their use in pregnancy. This problem has been particularly well characterized in the context of drug treatment in the US: data are insufficient to determine teratogenic risk for more than 98% of drugs approved by the US Food and Drug Administration (FDA since 2000, and 91% of drugs approved since 1980 (37,38). For nearly three-quarters of drugs approved since 2000, there are no human pregnancy data

whatsoever. Similarly, information to guide drug dosing is sorely lacking: more than 98% of pharmacokinetic studies done provide no data specific to use in pregnancy (37,38).

The dearth of evidence is due to many factors. One is the common practice of waiting to conduct reproductive toxicology, mutagenicity, and related studies until late in the R&D process when it is likely that the drug or biologic will proceed to licensure. This practice is an effective cost-management strategy but results in unintended downstream delays in understanding how the intervention works in pregnancy. Preclinical data are often critical to determinations of likely research-related risks and benefits of the intervention, required if pregnant women are to participate in clinical trials. These data also help to identify areas of potential concern or interest that should be pursued in research to further assess safety in pregnancy (39).

In large part, though, the lack of evidence to inform the use of preventives and treatments during pregnancy stems from a historical reticence to conduct interventional biomedical research with pregnant women. Helpful data on safety and efficacy can sometimes be gathered without involving pregnant women in interventional studies. However, there are many occasions when prospective enrollment of pregnant women, whether in small numbers to test pharmacokinetics or immunogenicity or in larger numbers to test safety and efficacy, can be critical to establishing an adequate evidence base.

Furthermore, the past practice in research oversight policies of categorizing pregnant women as “vulnerable” encouraged the view that the proper ethical stance towards research with pregnant women was exclusion, rather than careful and thoughtful inclusion (40). Other causes for this reticence include misinterpretations or overly cautious interpretations of what is allowed under research regulations and international norms, as well as concerns about legal liability (41,42). There are a range of cultural norms surrounding pregnancy and gender dynamics that complicate the involvement of pregnant women in research in various contexts. Pharmaceutical companies face disincentives relating to liability exposure, not only for trial-related risks but also post-approval liability that can be triggered if an indication is sought for use of an intervention in pregnancy (24,42,43). Finally, there are a number of risk distortions that have been noted with pregnancy, including, critically, the tendency to overweight the potential research-related risks to the fetus while ignoring the risks to the offspring of *not* allowing the pregnant woman into a study (44–46).

For all these reasons, pregnant women have been treated differently and, we have argued, unfairly in the development of new drugs and biologics (45,47,48). In contrast to other adults, little if any evidence about safety and efficacy for pregnant women is available at

the time of licensure. It is only well after licensure that evidence is usually generated, typically from clinical experience or passive surveillance systems (49–52).

Reliance on registries and other passive post-marketing systems is problematic. Selection biases in passive surveillance favor reporting of negative outcomes, and reports of adverse events may be incomplete (51–54). Although these systems are designed only to surface safety signals requiring further investigation, not to draw scientific conclusions, signals are sometimes over-interpreted as definitive evidence that a drug or biologic causes an adverse outcome (55). Perhaps most critically, relying on passive systems can lead to long delays in safety determination. In the US, it is estimated that the mean time it takes to assign a pregnancy-specific risk level to drugs with undetermined risk at the time of FDA approval is 27 years (37).

An increasing number of organizations, including the WHO, Pan American Health Organization (PAHO), Council for International Organizations of Medical Sciences (CIOMS), American College of Obstetrics and Gynecology (ACOG), and National Institutes of Health (NIH) Office of Research on Women's Health (ORWH), now recognize the importance, both scientifically and ethically, of involving pregnant women in research (40,56–59). They call for a shift in the presumption from exclusion to inclusion, while recognizing that research with pregnant women poses unique ethical complexities because of risks and potential benefits to future offspring who cannot consent for themselves. These organizations point out the analogy with and lessons from research with children: the need to include their distinct needs in the research agenda; the fact that there can be pathways to responsible inclusion; that access to trials involving the prospect of direct benefit can be important as a matter of justice; and the imperative to protect groups *through* research, not just *from* research.

Ethical Principles for Pregnant Women and Biomedical Research

As the importance of including pregnant women more adequately in the biomedical research agenda has solidified, four principles guiding research ethics for pregnancy have emerged as a growing consensus.

1. Pregnant women deserve an evidence base for the prevention and treatment of their illnesses equal to others as a matter of justice.

The foundational justification for this principle rests on the recognition that, because pregnant women are the moral equivalents of all other human beings and have equal moral standing, their interests and needs deserve to be treated fairly in the public investment in research. This principle has been reaffirmed in multiple international contexts, most recently by CIOMS in its explication of what just access to the benefits of research entails:

“Equity in the distribution of the benefits of research requires that research not disproportionately focus on the health needs of a limited class of people, but instead aims to address diverse health needs across different classes or groups. ... Since information about the management of diseases is considered a benefit to society, it is unjust to intentionally deprive specific groups of that benefit” (40). CIOMS explicitly includes pregnant women as such a group (40).

Just allocation of research investments to the health needs of pregnant women also accords with a core commitment of public health ethics to prioritize the needs of overly burdened and disadvantaged groups and to narrow unfair health disparities (60–62). Pregnancy often brings increased risk of illness and death and an often doubled health burden, to the woman and future child, especially in low- and middle-income countries and for poor women, globally (63–65).

2. Pregnant women should not be categorized as a “vulnerable population” for purposes of human subjects research review.

Until recently, pregnant women had been categorized as a “vulnerable population” for purposes of research regulations and guidance. This included, influentially, the US Federal Policy for the Protection of Human Subjects, which designated pregnant women as vulnerable alongside those whose capacity to make valid decisions about research participation is compromised, such as children and adults of limited cognitive ability (58,66). It was increasingly realized that such a designation was problematic, tacitly suggesting that pregnant women are incapable of offering valid consent (67–69). Further, the designation had unintended consequences of increasing health burdens: rather than safeguarding pregnant women and their future children from risk, it is now widely recognized that the categorization had the perverse result of adding risk to them by limiting the possibility of responsible research into their potentially distinctive health needs.

Both CIOMS and the Federal Policy for the Protection of Human Subjects have been recently updated to acknowledge that pregnancy itself does not make a woman “vulnerable” in the context of research participation. The revised 2016 CIOMS guidelines explicitly state that “pregnant women must not be considered vulnerable simply because they are pregnant,” (40) and the recently adopted updates to the Federal Policy for the Protection of Human Subjects confirm “the final rule no longer includes pregnant women... as examples of populations that are potentially vulnerable to coercion or undue influence,” effective January 2018 (40,70). While various factors can make specific pregnant women vulnerable, pregnant women as a group should not be characterized 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.

Like any research involving human subjects, research with pregnant women must meet all standard research protections: risk must be the least needed for scientific purposes, for instance, and appropriate informed consent must be obtained before research proceeds. Because it involves implications for potential offspring, there is widespread agreement that responsible research with pregnant women also requires added levels of distinct oversight for it to proceed (40,58). Most centrally are specific standards of what research-related risk is acceptable, especially to the fetus and future child, who cannot consent to those risks.

There are two different standards, depending on whether the trial in question offers the prospect of direct benefit to participants or offspring (see Box 2).

BOX 2 | PROSPECT VS. NO PROSPECT OF DIRECT BENEFIT

Trials involving the **prospect of direct benefit**—sometimes called “therapeutic research”—are those in which the study intervention may directly benefit the research participant. There is only a prospect of direct benefit, both because there is not yet confirmation of efficacy (that being one of the points of clinical research), and because, for trials with control arms, a given participant may not receive the experimental treatment being studied or an alternative intervention of proven benefit.

In contrast, studies with **no prospect of direct benefit** are those in which the possibility of benefit cannot reasonably be attributed. These studies include many early phase trials in which researchers have intentionally minimized the study intervention dose as a strategy to answer specific questions about safety, trials marked by too little evidence to reach a threshold of any reasonable prospect of benefit (even if benefits do accrue during the study), and studies whose focus is to better understand a point of biology rather than to test a potential preventive or therapeutic intervention. With studies that have no prospect of direct benefit, enrollment is purely for the value of advancing biomedical knowledge to the potential benefit of future populations and patients.

For trials that involve no prospect of direct benefit to either the woman or the future child, research-related risks to the future child are capped at a low risk threshold. In general, trials that do not carry any prospect of direct benefit to either the fetus or the pregnant woman can pose no more than “minimal risk” to the fetus, a standard commonly understood as comparing the probability and magnitude of anticipated harms with those ordinarily encountered in daily life or during the performance of routine physical or psychological

examinations or tests (40,70). Exceptions are given for research involving particularly compelling needs for the population of pregnant women and their infants: CIOMS allows a “minor increase over minimal risk” (40) and the Department of Health and Human Services (HHS) regulations carry a provision of increased risk under special HHS Secretarial review (70). While research involving no prospect of direct benefit to woman or future child can be important, it is not generally at issue in pregnancy and ZIKV vaccine research.

For trials offering the prospect of direct benefit to the pregnant woman, future child, or both, the standard of acceptable risk is importantly different. Rather than a specific threshold, acceptable risk is determined by the reasonability of the *relation* of research-related risks to the potential benefits offered by participation (71). The risk is justified by the anticipated benefits to the subjects. More specifically, the likelihood and importance of the potential benefits must be reasonably judged to outweigh the risks. These potential benefits must be at least as good as any available alternative preventive or therapeutic, as judged by a credible interpretation of available evidence, understanding that all such determinations will involve contexts of uncertainty (40).

There is no settled view about whether the prospect of benefit to the pregnant woman can justify an increment of research-related risk to the fetus. Important questions thus remain about how to proceed when interpreting acceptable fetal risk in research that carries the prospect of clinical benefit to the woman but none to the fetus. These questions are generally not relevant to ZIKV vaccine research, however, because both the pregnant woman, and especially her offspring, will experience the benefits if they materialize. In these kinds of cases, there is clear agreement that research that has a favorable potential risk-benefit balance (see Box 3) to the fetus can proceed so long as other protective regulatory standards are met.

BOX 3 | REASONABLE JUDGMENTS OF FAVORABLE RISK-BENEFIT BALANCE

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

4. Justice requires that pregnant women have fair access to research that offers the prospect of direct benefit.

The distinction between research involving the prospect of direct benefit and those that do not is also key to understanding another implication of the demands of justice as a core principle of research ethics; the importance of fair access to participate in research

involving the prospect of direct benefit (48,72,73). There is broad consensus that while biomedical research ethics includes the ethical imperative of protection *from* research harms and risks, it also includes the ethical imperative of fair opportunity to the benefits that participation in research can offer. Inclusion criteria for who is eligible for enrollment in research that offers a prospect of benefit must not unfairly exclude any group of persons or individual.

Fair opportunity to access the potential benefits of research participation stands as a critical ethical principle of justice that cannot be reduced to the scientific utility of a given population. Even in cases where it may not be scientifically necessary to include pregnant women in clinical trials to generate valid conclusions on the use of a product in pregnancy, pregnant women may still have compelling claims to participate in trials that offer the prospect of direct benefit to them or their offspring. This may be particularly true in the case of emerging infectious diseases and public health emergencies, when there are often few if any alternatives available for pregnant women to protect and preserve their health and that of their future offspring.

Fair access does not mean an automatic right to enrollment in all research involving the prospect of direct benefit. If a subpopulation does not meet the scientific eligibility requirements, or the risks of the trial are not in proportion to benefits for the group, then their exclusion is justified. Instead, fair access requires that a group must be judged eligible to participate so long as it meets general criteria of scientific relevance; that participation is otherwise allowable under applicable regulations and ethics guidance, including that there is a reasonable judgment of benefit favorable to risk; and that cost considerations do not suffice as a justification for exclusion.

Regulatory commentary and scholars in research ethics make clear that pregnant women are no exception to this principle (40,48,72,73). Pregnant women do not forfeit due consideration of how their health and interests could be advanced by participation in research simply because they are pregnant. More than that, in a great many cases, including ZIKV vaccine research, the benefits at stake with pregnant women's inclusion are benefits that accrue to two entities, not just one: the woman herself, as well as her offspring. 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 also entitled to treatment equal to other adults with regard to authorization of research participation. Fair access to research that offers a prospect of direct benefit requires that only the informed consent of the pregnant woman be solicited, and that her consent, alone, is sufficient to authorize research participation.

RECOMMENDATIONS

Over the course of our work, we came to consensus on three key imperatives, each with accompanying concrete recommendations. The first imperative and its recommendations address the importance of prioritizing and incentivizing development of a ZIKV vaccine that can be used by pregnant women. The second imperative and set of recommendations address the need for research specific to vaccine use in pregnancy for all ZIKV vaccines, with corresponding data collection efforts, in order to generate evidence that is critically needed to inform responsible public health policy and clinical practice affecting pregnant women. The third imperative and its recommendations address the importance of ensuring the fair inclusion of pregnant women in research studies carrying the prospect of direct benefit. These recommendations also take up best practices for involving key actors and experts in decision-making processes, responsibly communicating decisions and scientific findings to the public, and ensuring that pregnant women—as a class and as individuals—are given appropriate respect.

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.

Our first imperative concerns the ZIKV vaccine research and development agenda. Many ZIKV vaccines are currently being pursued. Not all are equally suitable for use in pregnancy, and not every ZIKV vaccine needs to be acceptable for use in pregnancy. Vaccines intended for routine childhood or early adolescent immunization, for example, are likely to be a critical component of the long-term response to prevent CZS. However, we believe it is essential that the ZIKV R&D community work collaboratively and expeditiously to develop vaccines that will be acceptable for use by pregnant women in the context of an outbreak.

Rationale

It now seems likely that, for years to come, ZIKV outbreaks and epidemics will periodically re-emerge throughout tropical areas where flaviviruses thrive (17,74,75). It is this likelihood that motivated the WHO to shift the designation from a Public Health Emergency of International Concern (PHEIC) to a focus on the long-term response to ZIKV as an “enduring public health challenge” (76). Whenever ZIKV outbreaks and epidemics occur,

pregnant women and their offspring will continue to risk the most dire consequences of infection.

In the initial efforts to coordinate R&D activities in response to ZIKV threats, the July 2016 WHO TPP called for development of vaccines targeted to women of childbearing age (WOCA) (77). While this population target was implicitly inclusive of pregnant women, and the TPP noted that the ideal vaccine would not be contraindicated for use during pregnancy, the failure to explicitly declare pregnant women as a target population that should be prioritized had some potentially harmful ramifications. Key stakeholders involved in ZIKV vaccine development interpreted the designation of WOCA without mention of pregnant women to mean that R&D efforts need not be inclusive of pregnant women—particularly with regard to research activities pre-licensure (78–80).

While immunizing adolescent girls and women before they become pregnant is a critical and necessary part of any overall ZIKV response, this strategy will not be sufficient to equitably address the needs of pregnant women and their offspring—those most at risk during a ZIKV outbreak. This has become increasingly clear as our understanding of the pathophysiology of the virus has evolved. At the time the first TPP was issued, it was hypothesized that the risks to the fetus were largely limited to exposure in the first trimester (81). This understanding provided only a very small window of time in which pregnant women could benefit from the primary value of a vaccine, prevention of CZS in their offspring. Moreover, in many contexts affected by ZIKV, women are often unaware of their pregnancies in the first trimester and unlikely to interact with the healthcare system until later in pregnancy.

However, growing evidence indicates that the critical risks of ZIKV infection to the pregnancy and fetal development endure well into the middle and later stages of gestation (2,6,82–84). Such serious and persistent risks suggest that offering immunization against ZIKV throughout pregnancy may confer significant benefits of risk reduction to pregnant women and their offspring. In light of this new evidence, failure to work toward a ZIKV vaccine that would be acceptable for widespread use by pregnant women as part of a key target population in an outbreak context is unjust and insufficient. It would unfairly deny possible benefits of a vaccine to pregnant women and their offspring. Moreover, it could lead to significant harms associated with large numbers of avertable cases of CZS.

In February 2017 the WHO updated their TPP for ZIKV vaccines for an outbreak response, stating: “It is an individual and public health priority to protect women throughout their pregnancy” (22). This update signals an important shift in thinking among global experts on ZIKV, vaccine development, and in maternal–fetal medicine on the importance of addressing the needs of pregnant women in the ZIKV vaccine response.

There are two additional ways that immunizing pregnant women may prevent harms. The antenatal period presents an important window of opportunity to reach many women who otherwise have little interaction with the healthcare system, and who may or may not have a facility-based birth. ZIKV vaccination in pregnancy could provide the added benefit of facilitating higher coverage rates among women of childbearing potential (WOCBP) to confer immune protection for subsequent pregnancies (26). This may be a particularly important strategy for reaching women who are among the most disadvantaged members of their society. It is also possible that vaccination during pregnancy could potentially confer immunity to the neonate and prevent postnatal infection (85). Limited data about the harms of early postnatal infection indicate the likelihood of a mild disease (86). However, some have suggested that malformations associated with late-pregnancy infection raise the possibility that ZIKV infection in newborns might lead to neurological damage (82). If future studies point to a serious impact from infection in infancy, conferred immunity may be an important benefit.

It is clear that a vaccine to prevent ZIKV infection holds significant potential to avert ZIKV-associated harms, and that pregnant women and their offspring should be able to share in the benefits of such a vaccine as a matter of justice. Past public health successes of maternal immunization have demonstrated the tremendous potential to reduce morbidity and mortality in mothers and their infants by extending the use of non-replicating vaccines developed and tested in non-pregnant adults for use in pregnancy (25). We should also learn from past experiences with diseases that cause congenital abnormalities, like rubella, and work hard to avoid a scenario in which the only licensed vaccines are ones that are contraindicated or otherwise not accepted for use in pregnancy because of the theoretical risk that replication-competent platforms could introduce the very harm they aim to prevent.

In the ZIKV response, we have the opportunity to build on the existing knowledge base of vaccine platforms and adjuvants in pregnancy to accelerate development of a ZIKV vaccine that will meet the needs of pregnant women in ZIKV outbreaks. Even with aggressive efforts to vaccinate women before pregnancy, we know from experience with other public health immunization efforts that 100% coverage rates will remain elusive. Some WOCBP will remain unvaccinated, especially in remote areas and among disadvantaged populations (87,88). In the absence of other effective modes of prevention or treatment, it is imperative that pregnant women at risk of ZIKV exposure, at all stages of pregnancy, have access to a vaccine to protect their own and their offspring's intertwined interests from the devastating consequences of congenital ZIKV infection.

ZIKV Vaccines that will be Acceptable for Use in Pregnancy

Developing a ZIKV vaccine that is acceptable for programmatic and clinical use in pregnancy (see Box 4) does not necessarily mean that the vaccine’s authorized label must include a specific indication for use in pregnancy. In fact, none of the vaccines currently recommended for use in pregnancy (e.g., by WHO Strategic Advisory Group of Experts on Immunization, ACOG, American Academy of Pediatrics) have such a specific label indication (89). In the US, because these vaccines are approved for healthy adults—a category that includes pregnant women—and do not contain a contraindication for pregnancy, programmatic recommendations for use in pregnancy are not considered inconsistent with FDA labeling (89). While a specific indication for use in pregnancy may be desirable for various ZIKV vaccines, especially in the long run, it may not be feasible in the nearer term given the rapid pace of vaccine development and the immediate need to get a vaccine to market.

BOX 4 | ACCEPTABLE FOR USE IN PREGNANCY

By **acceptable for use in pregnancy** we mean that relevant professional 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.

Determinations of acceptability will rely on evidence that these vaccines meet appropriate standards of safety with promising indicators they will be effective when administered in pregnancy. The acceptability threshold will rely upon various sources of data, including the vaccine platform’s history of use in pregnant women and, whenever possible, preclinical and human clinical trial data on the specific vaccine candidate. For instance, vaccine candidates that are not replication-competent, are unadjuvanted or use adjuvants with a track record of use in pregnancy (e.g., alum), with both sufficient evidence of efficacy and reassuring reactogenicity data from clinical trials with the broader adult population, and preferably also with pregnant women, are likely to meet the conditions to be acceptable for use in pregnancy.

It is also possible that, as R&D continues with more novel mRNA and DNA platforms, data will also support acceptable use of these types of ZIKV vaccines in pregnancy. Calls for data collection and evidence generation specific to safety and immunogenicity in pregnancy are further detailed under Imperative II and its corresponding recommendations, and this information will be critical for future determinations of which vaccines will be acceptable for use among pregnant women.

In addition to a promising risk-benefit profile, there will be other considerations relevant to ZIKV vaccine product development that will influence whether the vaccine is not only acceptable for use, but suitable to effective and timely administration in pregnancy. The number of doses needed to stimulate an adequate immune response and the schedule of administration will have important implications for whether a vaccine will be likely to offer protection during a current pregnancy. For instance, the development of a safe and efficacious ZIKV vaccine requiring three doses over six months would not adequately meet the needs of pregnant women as a target population because it would be unlikely to produce immunological protection within the critical window of exposure.

In summary, the intent of this imperative is to prioritize bringing ZIKV vaccines to market that have no contraindications for use in pregnancy and that clinicians and pregnant women can be comfortable using as an effective preventive intervention during a ZIKV outbreak.

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.

There are various mechanisms and processes that influence the kinds of products developed in response to emerging infectious diseases like ZIKV. As noted above, one key instrument being used to coordinate and advance global R&D efforts for a ZIKV vaccine is the WHO TPP, first issued in July 2016 and updated in February 2017 (22,77). The TPP identifies the target populations and describes the preferred and minimal product characteristics for vaccines aimed at protecting against congenital Zika syndrome in ongoing and future outbreaks. The TPP constitutes an important component of the WHO's "R&D Blueprint for Action to Prevent Epidemics," signaling the types of products that academic and commercial researchers should pursue and for which populations these interventions should be developed (90). We applaud the latest revisions to the TPP explicitly identifying pregnant women as a priority population for ZIKV vaccine development and encourage future revisions to retain, strengthen, and otherwise add language in support of this imperative throughout relevant sections of the document.

Funders of vaccine R&D, including public funders, multilateral funding mechanisms (e.g., UNITAID), and philanthropic organizations, also play a critical role in helping to ensure that the ZIKV vaccine landscape is inclusive of the needs of pregnant women. When issuing announcements and requests for proposals to support ZIKV vaccine development, key

funders can have significant influence explicitly identifying pregnant women as a priority population in these calls. One criterion for reviewing and issuing approval of applications submitted in response to these funding calls should be how well they address the interests of pregnant women as a priority population. The commitment to be inclusive of pregnant women as a priority population for ZIKV vaccine products can be reinforced at various points of review and feedback to applicants.

Other actors who by profession, position, or reputation can influence the direction of ZIKV vaccine development should also affirm and endorse the need for a vaccine that can appropriately be used during pregnancy. These include the leaders and spokespeople of public health agencies, research institutions, and manufacturing companies; political leaders driving government sponsored funding for ZIKV vaccine development; and leaders of public and private initiatives to coordinate ZIKV response efforts. Also important are the leaders and members of professional associations that are particularly engaged in the ZIKV response, including professional associations of obstetricians, maternal–fetal specialists, pediatricians, midwives, infectious disease specialists, pediatric neurologists, primary care clinicians, vaccinologists, and public health professionals.

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.

A coordinated response to global health emergencies and emergent threats requires significant investments of financial, technical, and programmatic resources—particularly when there are not existing interventions and the response entails financing the R&D pipeline for vaccines and therapeutics. Since the emergence of ZIKV in 2015, many of the major funders active in R&D for neglected tropical diseases have mobilized capital for ZIKV vaccine research, with funding announcements and significant awards issued by the NIH, US Biomedical Advanced Research and Development Authority (BARDA), the EU Horizon 2020 program, and the Wellcome Trust, among others (21,91). These awards include direct funding to researchers developing ZIKV vaccine candidates, support for building manufacturing capacity and infrastructure to produce and deliver vaccines, and investments in clinical research networks to support collaboration among and coordination across researchers. The rapid mobilization of resources to support ZIKV vaccine R&D has been impressive. Yet in fast-paced efforts to allocate resources for the immediate response, it

may be easy to overlook the additional resources required when including attention to pregnancy in the product development plan.

Development of a ZIKV vaccine that will be acceptable for use in pregnancy may require additional financial resources, particularly when this entails reproductive toxicology studies, collection and analysis of specific data on maternal, fetal, newborn, and child outcomes and indicators, and costs associated with both short- and longer-term follow-up of all women who are or become pregnant over the course of the trial and their offspring (43,92). Trials may also include provision of ancillary obstetrical care to pregnant trial participants. As key drivers of ZIKV vaccine research efforts, funders are not only in the position to allocate resources in support of vaccine candidates most likely to meet the needs of pregnant women, but should strongly consider the need for additional funds to cover costs of research inclusive of pregnant women and pregnancy-specific parameters. (Further details on what kinds of additional data and studies may be needed are provided under Imperative II, below.) For vaccine candidates that look promising for pregnant women, vaccine research groups and their sponsors should work closely and proactively with the appropriate regulatory agencies to determine what kinds of reproductive toxicology and/or pregnancy-specific data on maternal, fetal, and child outcomes will be necessary to determine the acceptability of a vaccine in pregnancy. This will help ensure timely and adequate allocation of resources to support the research activities important to meeting acceptability standards for use in pregnancy.

There are also a range of non-monetary inputs that can facilitate development of a ZIKV vaccine that would be acceptable for use in pregnancy. Research groups working on ZIKV vaccine candidates may not have much experience conducting trials inclusive of pregnant women or the collection of data specific to vaccine use in pregnancy, particularly if their past work addressed diseases for which pregnancy was not as central to the primary outcomes of interest. These groups could benefit from technical support and/or capacity building efforts on how to develop and implement trials that collect indicators relevant to maternal, fetal, and child safety and efficacy and on how best to include pregnant women as participants when appropriate. Collaboration and shared learning with those experienced in vaccine trials for maternal immunizations could represent an important in-kind resource. Various in-kind contributions, both those specific to developing a product for use in pregnancy and more general to the broader ZIKV vaccine R&D enterprise, can improve the timely development of an efficacious and safe vaccine for pregnant women.

Available resources, financial and otherwise, can and should be leveraged in support of developing ZIKV vaccines that will best meet the needs of pregnant women and their offspring.

Some mechanisms already exist that can be used to support development of ZIKV vaccine products for use in pregnancy. For instance, BARDA, which has committed significant resources to ZIKV vaccine development (in partnership with Walter Reed Army Institute of Research and NIH and through awards to Sanofi, Moderna, Takeda [93]) already has a mandate to support studies evaluating the safety of medical countermeasures in pregnancy under the US Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy and Implementation Plan 2016.³

PHEMCE affirms the commitment to ensure the needs of at-risk individuals—including pregnant women and children—are adequately addressed in emergency responses. Additionally, it offers non-monetary supports through the establishment of a cross-cutting integrated program team dedicated to addressing pediatric and obstetric populations (94). These and other global mechanisms supporting the ZIKV response, ZIKV vaccine development, and public health emergency (PHE) preparedness and response more broadly should be leveraged in support of R&D efforts that will yield a ZIKV vaccine that can be responsibly and effectively used in pregnancy.

BOX 5 | CONSIDERATIONS FOR IMPLEMENTATION OF RECOMMENDATION 2

- » When funders make decisions about the amount of financial resources they award to vaccine researchers working on ZIKV vaccine products that have a reasonable expectation of use in pregnancy, it is important to consider what additional resources might be required to allow trials to be inclusive of or responsive to pregnant women’s needs and to allocate sufficient resources to cover those projected costs as part of a comprehensive funding award.
- » Biotechnology firms, pharmaceutical companies, contract research organizations (CROs), and other industry members who are in a position to offer in-kind support to facilitate the work of research groups conducting trials of ZIKV vaccine candidates expected to be acceptable for use in pregnancy should consider what non-monetary supports they can provide to these research groups. Those with experience conducting research with pregnant women can offer in-kind supports specific to vaccine trials with pregnant women. In-kind supports may include:
 - » Technical assistance for trial design and implementation when including

³The PHEMCE is an interagency coordinating body led by Health and Human Services Assistant Secretary for Preparedness and Response and comprised of the CDC, NIH, FDA, and interagency partners at the Departments of Veterans Affairs, Defense, Homeland Security, and Agriculture. It coordinates the development, acquisition, stockpiling, and use of medical products that are needed to effectively respond to a variety of high-consequence public health emergencies.

- obstetric populations or outcomes
- » Donation of equipment (e.g., ultrasounds) or diagnostics
- » Provision of expertise on pregnancy-specific parameters of normalcy
- » Training of research staff and lab technicians
- » Trial networks, research groups, collaborative networks, and data-sharing initiatives can promote the sharing and availability of tools and resources that will support the development and implementation of trials for ZIKV vaccine candidates that would be acceptable for use in pregnancy. Resources may include:
 - » Repositories of sample protocols for maternal immunizations
 - » Open data on previous use of vaccine platforms or adjuvants in pregnancy

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.

The legal and financial interests of ZIKV vaccine developers are intertwined. Those interests can work together to create disincentives to develop ZIKV vaccines that would be acceptable for use in pregnancy, but they also can be used to incentivize such development. Policymakers, regulatory authorities, sponsors, funders, and those who are positioned to influence ZIKV vaccine research and outcomes should work together to identify global and country-specific incentives and disincentives for ZIKV vaccine development and pregnancy.

R&D of a ZIKV vaccine requires a dedicated multinational effort, from vaccine concept to ultimate distribution and administration. Development of a vaccine may involve multiple clinical trial sites and approval, licensing, and manufacturing processes that may take place across several different countries. Because each of those processes is subject to country-specific regulation and oversight, vaccine development and approvals can be legally complicated. Additional laws may apply in countries that have declared ZIKV a PHE, regardless of whether other countries or global organizations have an active designation of ZIKV as a PHE. For example, while the WHO no longer considers ZIKV to be a PHEIC under

the International Health Regulations, the United States and several individual US states continue to treat ZIKV vaccine R&D under specific public health emergency laws. All these layers of legal complexity must be taken into consideration when analyzing incentives and disincentives to develop a ZIKV vaccine that will be acceptable for use in pregnancy.

Special attention should be given to existing, country-specific legal and financial incentive mechanisms and how quickly they can be operationalized, as well as whether particular incentives for vaccine development exist during declared PHEs. International collaborative arrangements among national regulatory authorities—for example, through the International Coalition of Medicines Regulatory Authorities (ICMRA) and the International Conference of Drug Regulatory Authorities (ICDRA)—may be helpful in coordinating and harmonizing regulatory requirements, which together can accelerate product development and distribution.

Various mechanisms with proven international success in incentivizing product development exist (see Box 6). They have the potential to lower development costs, and for the private sector, to also increase financial profit and cultivate early brand recognition and allegiance, ultimately benefiting market share and assuring product development for those in need (95,96). These mechanisms should be explored for their potential to create incentives to promote the development of ZIKV vaccines that will be acceptable for use in pregnancy, and implemented whenever possible.

BOX 6 | INCENTIVE MECHANISMS TO STIMULATE R&D

- » Exemption from regulatory fees
- » Priority regulatory review and/or vouchers
- » Accelerated regulatory approval
- » Research and development tax credits
- » First-to-market or earlier market entry
- » Extended and/or longer duration of market exclusivity
- » Expedited patent review
- » Extended and/or longer active patent protection
- » Advance market commitments and other guaranteed product purchase programs

There are a number of programs at the international and national level that use one or more of these incentives. Programs may differ as to whether they offer immediate, short-term, or long-term financial or legal benefits that can motivate vaccine developers to be

inclusive of the interests of pregnant women. Their availability and function may depend on the existence of a declared public health emergency.

For example, regardless of a declared PHE, the FDA has a number of mechanisms to expedite the review and approval of drugs and biologics that address serious conditions and unmet medical needs (97). The FDA also has a Priority Review Voucher (PRV) program through which applicants seeking FDA approval of products for certain tropical diseases, certain rare pediatric diseases, and medical countermeasures may apply to receive a priority review voucher for future products (97–102). The FDA issues the voucher once the eligible product is approved. These vouchers are considered especially valuable because they not only offer priority review of a future product, but can also be sold or transferred.

Products related to ZIKV, presumably including those vaccines that would be considered acceptable for use in pregnant women, are eligible under the tropical disease PRV program. Additionally, during a declared PHE, the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) codifies and builds on the FDA's ongoing efforts to enhance review processes and advance regulatory science for development of medical countermeasures (103). The European Medicines Agency (EMA) also has a mechanism for accelerated assessment of interventions addressing unmet medical needs, with additional technical supports to leverage this mechanism through the PRiority MEdicines (PRIME) scheme (104). Where applicable, other incentive mechanisms such as tax credits and advance market commitments should be explored.

Implementing incentive structures to promote R&D of ZIKV vaccines that will be acceptable for use in pregnancy is not enough. It is also important to simultaneously address potential disincentives. One set of disincentives concerns the legal and financial risks of conducting research with pregnant women, in particular those associated with potential research-related injuries to the pregnant woman or her future offspring. Trial insurance, indemnification, and compensation programs can mitigate those risks by anticipating and covering possible research-related harms to the pregnant woman, fetus, and child subsequently born from that pregnancy. During declared public health emergencies, governments may provide or authorize some or all of those programs, which can substantially offset the perceived legal and financial disincentives of conducting research with pregnant women. HHS, for example, has declared that certain ZIKV vaccines⁴ are "covered countermeasures" under the Public Readiness and Emergency Preparedness Act

⁴ 42 U.S.C. 247d–6b(c)(1)(B), 42 U.S.C. 247d–6d(i)(1);(7). "Covered countermeasures are the following Zika Virus vaccines, all components and constituent materials of these vaccines, and all devices and their constituent components used in the administration of these vaccines: (1) Whole-particle inactivated virus vaccines, (2) Live attenuated vaccines, (3) mRNA vaccines, (4) DNA vaccines, (5) Subunit vaccines, (6) Peptide vaccines, (7) Virus like particles vaccines, (8) Nanoparticle vaccines."

(105,106). That legally authorized administrative action has the effect of providing liability immunity to particular individuals and entities (such as vaccine manufacturers) against liability claims arising from the administration of covered ZIKV vaccines in research. It also provides compensation under the Countermeasures Injury Compensation Program to individuals—including pregnant women and offspring that were in utero at the time of vaccine administration and are subsequently born—who suffer previously specified, serious physical injuries from receiving covered vaccines, whether in research trials or through emergency response efforts.

It is also possible that those responsible for conducting ZIKV vaccine R&D may be discouraged from including pregnant women in research activities due to potential liabilities associated with use by pregnant women *after* the product is authorized. Vaccines approved for use in women of reproductive age have often included precautionary language in package inserts and product labels regarding product use in pregnancy. This precautionary language may have the effect of shifting liability risk from manufacturers and regulators to healthcare providers.⁵ Regardless, the language usually co-travels with the absence of any pre-approval data on vaccine use in pregnancy. Vaccine injury compensation programs are a potential strategy to address this misalignment of incentives and disincentives. The US Vaccine Injury Compensation Program (VICP)⁶ was introduced, in part, to ensure continued investment in the development and manufacturing of childhood vaccines by removing liability once the vaccine is in use, and has been associated with statistically significant increases in clinical trials for new childhood vaccines (107).

Although there are no assurances that ZIKV vaccines under development will be covered under the VICP or other similar vaccine injury compensation programs in other countries, the existence of and potential eligibility for compensation schemes may help mitigate market disincentives toward the development of ZIKV vaccines acceptable for use in pregnancy (108). ZIKV vaccine developers should engage early on with the relevant authorities and committees that administer, oversee, and make recommendations and

⁵ The 2015 FDA's Pregnancy and Lactation Labeling Rule (PLLR) now requires pharmaceutical companies to include on product labels more detailed information, where available, on the potential risks and benefits of drugs and biologics in pregnancy, with updates to the label when new information becomes available. It is unclear to what extent this will affect the inclusion of general precautionary language surrounding product use in pregnancy on the label alongside required categories of data on the label.

⁶ For a vaccine to be covered by the VICP, it must be FDA approved, part of a category of vaccines recommended for routine administration to children or pregnant women by the US Centers for Disease Control and Prevention (CDC), subject to a federal excise tax, and added to the VICP by the US Secretary of Health and Human Services. The 21st Century Cures Act (2017) expanded the types of claims that may be filed under the VICP to include not only injuries allegedly suffered by a woman who received a VICP-covered vaccine during pregnancy, but also injuries allegedly sustained by her offspring who were in utero at the time she received the vaccine. It continues to exclude research-related injuries.

determinations on vaccine eligibility for existing injury compensations programs to determine the potential for their product to be covered under these schemes.

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.

The importance of intentionally and proactively obtaining data on safety and immunogenicity in pregnancy for all ZIKV vaccine candidates targeted to women of childbearing potential (WOCBP) cannot be overstated. These data will be critical for public health officials, clinicians, and pregnant women to make informed decisions about both the use of ZIKV vaccines during pregnancy and the proper response when pregnant women are unintentionally immunized during a vaccine rollout in a ZIKV outbreak or in a ZIKV prevention program. The types of pregnancy-specific research questions that should be pursued, as well as methods and timing of data collection activities, will vary for each vaccine candidate. In particular, these activities will depend on: (1) the characteristics of the vaccine candidate and platform; (2) existing evidence and knowledge gaps on use of the platform and/or adjuvant in pregnancy; (3) existing evidence from and knowledge gaps in preclinical and other studies on the specific candidate; (4) any theorized differences in safety or efficacy of a vaccine candidate in pregnancy based on the relevant biological mechanisms; and (5) whether the data are meant to inform widespread intentional use in pregnant women or provide information about potential risks associated with unintentional use.

Regardless of which research questions are relevant, it is imperative that proactive plans are developed and pursued to generate needed evidence to address those questions as early as possible. The collection of data on safety and immunogenicity in pregnancy for promising ZIKV vaccines is critical for at least two reasons: (1) to ensure responsible, timely, and evidence-informed decisions about intentional use of ZIKV vaccines in pregnancy and (2) to support responsible management of inadvertent exposure to ZIKV vaccines during pregnancy.

1. Ensuring responsible decisions about, and timely adoption of, ZIKV maternal immunization.

Imperative I outlined the need for including pregnant women as a specific target population for ZIKV immunization designed for outbreak situations and thus why the global research community should work to develop ZIKV vaccines acceptable for use in pregnancy. Determining which ZIKV vaccines should be adopted for this target population will rely on available evidence to assess potential risks and benefits of the vaccines products. It is therefore critical that researchers and manufacturers proactively devise and pursue intentional plans to gather, generate, and analyze the needed safety and immunogenicity data specific to use in pregnancy. These data should be obtained as early as possible in the clinical development plan, with follow-on studies to further pursue knowledge gaps on safety and efficacy in larger samples of the population.

It might seem self-evident that data indicative of safety and efficacy in pregnancy, especially for a vaccine that pregnant women are likely to use or be exposed to, would be collected prior to endorsing a vaccine for use in pregnancy in a public health program. Historically, however, recommendations for the use of vaccines in pregnancy have gone forward without data about benefit or risk of the specific vaccine to pregnant women and their offspring, or they have been based on post-licensure study and data collection efforts, largely through pregnancy registries and rarely with well-designed trials or observational studies (89,109).

This approach to explore safety, immunogenicity, and efficacy in pregnancy only after product licensure can come at significant cost. It can limit vaccine acceptance, both at the point of policy adoption and recommendation (110,111) as well as among obstetric providers who are “unsure about making strong recommendations for maternal vaccinations [given the] limited understanding of the immunogenicity and safety of vaccine delivery during pregnancy” (35). Acceptance of vaccinations by pregnant women is strongly associated with provider recommendations (111–113). From experience with other vaccines, we know that reliance on post-licensure and observational data can further reduce appropriate access by feeding mistrust and concerns about safety of products among clinical providers and patients (114). The delay in evidence has led to significant lags in recommended use of vaccine products in pregnancy that could have averted serious illness or death among hundreds of thousands of mothers and infants (see Box 7).

BOX 7 | PERTUSSIS VACCINATION AND THE COSTS OF DELAYED STUDY AND USE IN PREGNANCY

Vaccines protecting against pertussis have been in use for decades, with new Tdap formulations of the vaccine licensed in 2005. However, it was not until 2011 that the US CDC’s Advisory Committee on Immunization Practices (ACIP) recommended the use of Tdap in pregnant women who

had not previously been vaccinated, when it became clear that alternative approaches to vaccinate around and after pregnancy were insufficient for reducing infant morbidity and mortality (181). Between 2004 and 2010 the CDC reported an average of 3,055 infant pertussis cases per year with more than 19 deaths annually. When this number rose to an estimated 41,880 cases in 2012, the ACIP expanded their recommendation for use in all pregnancies and not only those without prior vaccination (181). Earlier investigation of the safety and efficacy of Tdap in pregnancy could have accelerated ACIP's decision to recommend the vaccine, well ahead of the surge in infant pertussis cases. The failure to prospectively plan and implement studies of Tdap in pregnancy means that, to this day, critical questions specific to use in pregnancy remain unanswered regarding vaccine effectiveness, optimal timing of vaccine administration, infant antibody correlates of protection, and the safety of repeated dosing in women who become pregnant again shortly after the last pregnancy during which they were immunized.*

**Current studies are underway to further explore questions about Tdap in pregnancy.*

The changes that pregnancy can induce in the maternal immune system provide yet another important reason for studying vaccines in pregnancy. The failure to explore potential differences in immunological response to vaccines administered in pregnancy and the impacts this may have on their efficacy can result in inadequate guidance on the appropriate use of vaccines by pregnant women.⁷ In the case of ZIKV, data on the immunological response may be important for determining adequate dosing for pregnant women, including whether and when a booster may be needed to ensure protection against ZIKV across future pregnancies (115).

Traditional post-approval approaches to gathering evidence on safety, immunogenicity, and efficacy of vaccines in pregnancy may also be logistically problematic in the case of ZIKV because of the waxing and waning of ZIKV outbreaks. ZIKV vaccine developers and public health officials have already noted that a decline in ZIKV transmission—while good for public health and those living in affected regions in the near term—may present challenges in determining which ZIKV vaccines are truly effective before the next round of outbreaks (116). If the high rates of ZIKV in active areas are still declining when the earliest candidates move to planned Phase II and III trials, and we fail to capture data on the safe and effective

⁷ While some studies of vaccination in pregnancy have shown equivalent immunological responses in pregnant and non-pregnant women, other studies of vaccines including for hepatitis B, influenza, pertussis, and yellow fever have demonstrated lower immunogenicity in pregnant women than in non-pregnant women (23). These findings of altered immunogenic response did not, however, translate into decreased clinical effectiveness.

use of ZIKV vaccines in pregnancy amidst this wave of circulating wild type ZIKV, there may not be another opportunity to collect certain kinds of critical data on use in pregnancy until the next wave of large-scale outbreaks.

Moving the ZIKV vaccine research agenda forward in the intervening years of sporadic or low-grade ZIKV clusters will require relying on endpoints like correlates of immunity rather than prevention of clinical infection (117). Given our current limited understanding of maternal–fetal physiology and immunology, including the immunological role of the placenta, it could be difficult to draw firm conclusions on the effectiveness of the vaccine in pregnancy based on correlates of immunity established in non-pregnant adults (35).

Although there are reasons to think that a vaccine that produces a strong enough immunological response in non-pregnant women will also be protective in pregnant women, there is limited data to inform what would constitute a sufficient level of immune response in the pregnant body to adequately protect against the harms of ZIKV infection. These uncertainties underscore the importance of including pregnant women as early as possible in efficacy trials of ZIKV vaccine products expected to be appropriate for use in pregnancy and of capturing data from unintentional exposures of pregnant women in all ZIKV vaccine trials so as not to miss a critical opportunity to gather evidence on immunogenicity as well as safety.

Having an evidence base to inform judgments on safe and effective use in pregnancy will also help decision-makers in the event that multiple efficacious ZIKV vaccines are approved for use. It is likely that public health agencies or programs delivering vaccines will adopt only one or two vaccine products for their entire target population. With pregnant women and WOCBP comprising an important subset of that target population, it will be critical for policymakers to have evidence specific to use in pregnancy to assess the comparative advantages and disadvantages of the available vaccine products.

2. Responsible management of inadvertent exposure to ZIKV vaccines during pregnancy.

For vaccines anticipated to be used by pregnant women, there is a clear and compelling need for evidence that can inform judgements about safety and efficacy in pregnancy. But it is also critical to collect evidence to inform judgments of safety and efficacy in pregnancy for vaccines *not* currently anticipated to be acceptable for use by pregnant women.

Given that WOCBP will be a primary target population for ZIKV vaccine programs, it is inevitable that sizeable numbers of women will be vaccinated not knowing that they are pregnant, or will become pregnant soon after vaccination. The predictable exposure of significant numbers of pregnant women who will not know their pregnancy status at the

time of vaccination underscores the importance of obtaining at least preliminary data about fetal risk and maternal immunogenicity (including durability) for any vaccine targeted at WOCBP. This is especially the case for live attenuated ZIKV vaccines. Although we have yet to see serious risks manifest with other live vaccines inadvertently given in pregnancy, there remain deep concerns about the theoretical and biologically plausible risk of a live attenuated ZIKV vaccine causing CZS. Concerns may also exist about non-replication-competent ZIKV vaccine candidates that have uncharacterized risks in pregnancy or for which there is limited understanding or evidence of potential harms, such as those using novel adjuvants or platforms.

This point is worth underscoring. Prior experience of other public health rollouts in WOCBP indicate the potential for significant rates of inadvertent exposure. For instance, because pregnancy tests are not often used in during mass vaccination campaigns (which instead typically rely on self-reported pregnancy status), thousands of pregnant women have been inadvertently vaccinated with the inactivated meningococcal conjugate vaccine, as well as with the live attenuated rubella vaccine and the live attenuated yellow fever vaccine (109). Inadvertent exposure of pregnant women may be especially prevalent with ZIKV vaccine, given WHO indications that in order to maximize vaccination rates, pregnancy testing prior to vaccine administration in resource-poor, ZIKV-affected areas may not be feasible or advisable (22).

The price of ignorance in the face of unintended exposures is significant. In the case of rubella vaccination, hundreds of women inadvertently exposed to the vaccine terminated their pregnancies, presumably due to concerns about unknown fetal harm (118–121). The Vaccine Adverse Events Reporting System has documented pregnancy termination after vaccination across platforms as recently as 2006, despite CDC assurance that “risk for a developing fetus from vaccination of the mother during pregnancy primarily is theoretical,” and that inadvertent vaccination “should not ordinarily be a reason to consider termination of pregnancy” (122). Further, pregnant women who are inadvertently vaccinated will want to know not just whether the vaccine is safe, but how likely it is that the vaccine they received will protect them and their fetus from infection. Such information may guide decisions about how aggressively to pursue other protective measures such as mosquito nets and repellent, condom-protected sex, and travel restriction, and whether they should pursue a vaccination booster post-delivery to have protection in future pregnancies.

Unintended exposures may also be likely in large-scale efficacy trials of ZIKV vaccines, particularly if it is not feasible to screen for pregnancy. The experience with recent dengue trials is instructive here, as there were significant unanticipated inadvertent pregnancy exposures, with 613 total unplanned pregnancies in all CYD Dengue Vaccine trials, 402 of

whom were in the intervention arms (123). These numbers included unintended exposures in which women enrolled in trials became pregnant soon after administration of the vaccine, notwithstanding counseling to avoid pregnancy for a specific window after exposure.

Because unintended pregnancy exposure to ZIKV vaccines targeted to WOCBP is both predictable and likely to be extensive, the research and public health communities have a responsibility to pursue evidence that will allow for the best possible counseling on the implications of that exposure. Appropriate interpretation of data from inadvertent exposures will entail careful attention to, and possible data collection on, the background rates of adverse pregnancy or birth outcomes. These data are needed to determine whether any adverse outcomes among those exposed inadvertently occur at an elevated rate compared to the general population of unexposed pregnant women.

Furthermore, given the likelihood of widespread inadvertent pregnancy exposures during mass vaccination campaigns, health ministries will need data about the profile of fetal risks attendant to given vaccines, as early as is feasible, to guide their decisions about which vaccines to adopt, and the circumstances of their use. Having data that are as reflective of actual risk as possible, as early as possible, will help public health officials, vaccine program leaders, and funders make the best decisions about key issues such as which vaccines to invest in and whether allocating resources to pregnancy testing is warranted. Even after ZIKV immunization efforts are underway, evolving evidence from inadvertent exposures in trials and post-licensure use may necessitate changes in practice or policy.

To ensure we have a timely and adequate evidence base to inform the intentional use of ZIKV vaccines in pregnancy as well as appropriate management of unintended exposures, it is imperative that clinical development plans for all ZIKV vaccine candidates intended for widespread immunization of women of childbearing potential adequately include indicators and outcomes to inform judgements on safety and efficacy in pregnancy.

To operationalize this imperative, we endorse the following recommendations:

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 the subset of vaccine candidates anticipated to be acceptable for use with pregnant women at risk of ZIKV exposures, it will be critical to have evidence to inform assessments of whether these products not only meet safety standards for use in pregnancy, but also assessments of their potential to induce sufficient immunological protection against the virus to prevent CZS. Both assessments will require the systematic collection of data specific to vaccine administration in pregnancy at relevant time points in the clinical development pathway, as well as extended plans to collect further data on critical research questions for which there will not be sufficient evidence from pre-licensure or pre-approval studies to draw firm conclusions.

The evidence required to draw scientific inferences and conclusions about safety and efficacy in pregnancy will be candidate-specific. However, any vaccine candidate expected to be acceptable for use in pregnant women would at minimum require reassuring safety data—including data on possible teratogenic effects and adverse pregnancy outcomes. Evidence of safety could draw upon multiple information sources, including safety data on the use of the platform and/or adjuvant in other vaccines administered in pregnancy, reproductive toxicology studies specific to that vaccine, data from pregnant women enrolled in Phase II and/or III trials, as well as data—including maternal, fetal, and infant outcomes—from trials in which there are inadvertent exposures in pregnancy. The types of safety data needed and the timing of their collection will depend on the kinds of theorized risks associated with giving the vaccine in pregnancy as informed by the mechanism of action and the existing safety data and knowledge gaps on the platform and candidate. Relevant advisory bodies and public health authorities may provide guidance on what they would need to endorse use of the ZIKV vaccine in pregnant women. For instance, in a 2015 report, the US FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) provided guidance on the clinical development of vaccines intended for use in pregnancy to prevent diseases in infants, including the relevant sources of safety and

efficacy data that would be expected for licensing a vaccine with an indication for use in pregnancy (124).

As noted above, the extent to which reproductive toxicology studies may be informative data sources for different vaccine candidates will vary based on the existing data on the platform, adjuvant, and other similar vaccines used in pregnancy. Nevertheless, certain kinds of reproductive toxicology studies may be requirements for the inclusion of pregnant women in efficacy trials and for regulatory authorizations of products. It will be important for study teams working on ZIKV vaccines anticipated to be acceptable for use in pregnancy to determine what types of reproductive toxicology data will be necessary to move forward with inclusive clinical development plans and to avoid delays in product authorizations.

Because many investigational vaccine candidates never advance beyond preclinical or Phase I trials, and because reproductive toxicology studies are a costly endeavor, it may be prudent to wait to initiate these studies until it seems likely that the candidate will move to Phase II trials. That said, having in place a funded plan and developed protocol to conduct needed reproductive toxicology and related subsequent studies can allow these studies to be initiated as soon as data from Phase I and/or animal challenge studies show significant promise that the candidate vaccine will move forward. This coheres with the recommendations from the WHO consultation group addressing regulatory considerations for ZIKV vaccine development intended for use in outbreaks, which suggested that reproductive toxicology may be necessary for product approvals and should be planned for early on in the clinical development plan to avoid delaying authorization (19).

It is also important to gather evidence on the effectiveness of any vaccine anticipated to be acceptable for use in pregnancy. Sources of evidence include data on immunogenicity and performance in non-human pregnant animals and non-pregnant adult women. There may be theoretical or other reasons to conclude that the mechanisms of action and resulting immunoprotection in non-pregnant women will be predictably similar in pregnant women. That said, data on immunogenicity in pregnant women and their offspring—with immunologic bridging and/or efficacy studies—offer the most direct and relevant evidence.

For trials of candidates anticipated to be acceptable for use in pregnancy with promising preclinical, Phase I and IIa studies, there is no compelling justification for not including pregnant women in subsequent efficacy studies. Including a cohort of pregnant women in efficacy trials need not extend the duration of the trial and thus will not delay the time to public health delivery. While there will not be a sufficient number of pregnant women enrolled in these trials to determine efficacy in preventing CZS, their prospective inclusion in these studies will provide critical and timely information on immunogenicity and other

correlates of immunity, as well as what is likely to be reassuring data about vaccine safety. However important, data collected from non-pregnant women participating in ZIKV vaccine trials will not be an appropriate or adequate substitute for the kinds of data that can be obtained from pregnant women who are prospectively enrolled in efficacy trials.

Additionally, because all trials enrolling WOCBP are likely to have some subset of women inadvertently vaccinated in pregnancy or becoming pregnant within a critical window following vaccination, there should be a prospective plan for systematic observational studies to gather data from them and their offspring to inform key questions on safety, immunogenicity, and efficacy. Capturing data from women who are inadvertently immunized with a ZIKV vaccine candidates in pregnancy will not only increase the total amount of evidence relevant to safe and efficacious use in pregnancy that can be generated from trials, but it will also enable collection of data from vaccine administration occurring earlier in gestation than may be possible in a trial prospectively enrolling pregnant women. This will provide a more comprehensive understanding of the effects of a ZIKV vaccine candidate across the dynamic stages of pregnancy.

A number of resources have been developed in recent years to provide guidance on the protocol design and safety assessments for research on vaccines anticipated to be used in pregnancy (35,39,124–145). Though not specific to the special case of public health emergencies or ZIKV, these resources provide useful guidelines on data that would be ideally acquired prior to enrolling pregnant women in vaccine trials, attention to the definition and assessment of safety parameters and adverse events in pregnancy, and protocol development and sequencing of reproductive toxicology studies to allow timely enrollment of pregnant women in studies.

BOX 8 | IMPLEMENTATION CONSIDERATIONS, RESOURCES AND BEST PRACTICES FOR RECOMMENDATION 4

Categories of data most relevant to inform assessments of safety and efficacy of ZIKV vaccines in pregnancy include:

SAFETY

- » Data on pregnancy outcomes and fetal safety
- » Birth outcomes and relevant longer-term infant child outcomes (2–5 year follow-up)
- » Maternal outcomes, including rates of and outcomes from GBS
 - » Population and ZIKV infection-specific background data on adverse pregnancy and birth outcomes to reduce likelihood of misattribution of harms to vaccines

IMMUNOGENICITY

- » Immune response in pregnancy post-vaccination (for each dose administration)
- » Durability of immune response and antibody waning
- » Exploration of significant differences between pregnant and non-pregnant women's immunological responses post-vaccination
- » Exploration of effect of gestational age on immunogenic response
 - » Note: some if not all immunogenicity data in early pregnancy will come from opportunistic data among participants who fall pregnant on trials, since those enrolling when pregnant may already be several weeks into their pregnancy before they become aware of their pregnancy status
- » Transplacental transfer of ZIKV antibody (with regard to gestational age)

EFFICACY AND EFFECTIVENESS (LIKELY IN POST-APPROVAL STUDIES)

- » May require bridging studies to confirm earlier indicators of efficacy based on correlates of immunity
- » Prevention of CZS
 - » It will be important for those working on the R&D of ZIKV vaccines anticipated to be acceptable for use in pregnancy to work with relevant regulatory authorities and agencies to identify data requirements for their candidate based on its specific characteristics
- » This includes identifying what data would be needed to enable prospective inclusion of pregnant women in trials as well as establishing a systematic approach for classifying adverse events in pregnant women and infants ahead of enrolling pregnant women in trials
- » This will also help identify any incremental costs associated with developing a ZIKV vaccine acceptable for use in pregnancy to enable procurement of additional funding resources. Additional costs may be associated with: reproductive toxicology studies, additional clinic visits among pregnant participants; additional collection, processing, and analysis of specimens; provision of obstetrical care and other ancillary care; personnel or consultant costs to have relevant expertise for maternal-fetal trial design and interpretation of findings. These should be pursued supported under comprehensive funding awards (See Recommendation 2)
- » Vaccine researchers working on ZIKV vaccines anticipated to be acceptable for use in pregnancy should develop standard, harmonized outcomes and endpoints of interest related to maternal, fetal, and infant safety and immunogenicity to support more valid conclusions across studies of different candidates and leverage mechanisms to foster collaboration and knowledge-sharing

- » Some mechanisms to support harmonization already exist (e.g., GAIA, PHEMCE online portal: www.medicalcountermeasures.gov, ZIKAplan)
- » Various strategies exist to appropriately stage the timely collection of pregnancy-specific data (e.g., those discussed in Baylis and Halperin’s “Trials and Tribulations” piece)
- » Open data on previous use of vaccine platforms or adjuvants in pregnancy

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.

It is hopeful that a number of ZIKV vaccines authorized for use, whether through traditional or accelerated authorization pathways, will be *deemed acceptable for use in pregnancy* in a ZIKV outbreak. Although this means there will be sufficient preliminary information to support the use of these vaccines in pregnancy, questions are likely to remain regarding immunogenicity and effectiveness of these ZIKV vaccines in pregnancy as well as the full safety profile. This is in part because knowledge of the virus’s pathophysiology and immune system interactions is still limited, and most ZIKV vaccines are likely to be approved using surrogate endpoints, such as correlates of immunity (22,146). Even when investigators test ZIKV vaccine candidates among a cohort of pregnant women and/or collect data from inadvertent exposures of pregnant women in trials, sample sizes will not be sufficient to determine efficacy in pregnancy. There may also be outstanding questions on how immunogenicity could vary in pregnancy based on dosing and when during the pregnancy vaccine administrations occur. Additionally, some safety signals may emerge only when the product is used by much larger numbers of pregnant women than can be enrolled in an efficacy trial. For vaccines that will be intentionally administered to pregnant women, it will be critical to develop a fuller evidence base on their safety and effectiveness in pregnancy than can

be obtained even in efficacy trials that collect data on pregnant participants and their offspring.

This need underscores the importance of continued investment in and prospective planning for research to investigate important pregnancy-specific research questions after a ZIKV vaccine is in use. There are a range of approaches that can be utilized for ongoing gathering of evidence on specific indicators and outcomes relevant to safe and effective use in pregnancy—for both the mother and future offspring. These include adverse event reporting systems, prospective and retrospective observational studies, clinical trials,⁸ post-marketing surveillance, and pregnancy registries.

If carefully designed, executed, and analyzed, post-authorization studies can provide critical information for the optimal and appropriate use of ZIKV vaccines in pregnancy. The European Medicines Agency (EMA) includes in their Good Pharmacovigilance Practices (GVP) a “Guideline on the exposure to medicinal products during pregnancy: Need for post-authorisation data”(147) and the Agency plans to release a new population-specific chapter for Pregnant and Breastfeeding Women for public consultation later in 2017 (148). Similarly, the FDA provides some limited guidance for industry on post-marketing studies and clinical trials (149). A recent article authored by GlaxoSmithKline employees provides the manufacturer perspective on how to strengthen safety studies conducted post-approval (150). The authors identified some challenges in conducting post-authorization safety studies for vaccines, including examples assessing vaccine safety in pregnancy, as well as some solutions for establishing appropriate comparator groups, determining feasible options to fulfill study objectives, and reducing potential sources of bias that would misattribute harms to vaccine exposure. Other resources specific to generating and harmonizing safety data for vaccines in pregnancy—including in Phase IV studies—are available from the GAIA project (Global Alignment of Immunization Safety Assessment in Pregnancy) and The Brighton Collaboration (126,127,151). These resources and guidelines should be leveraged in developing post-authorization studies and pharmacovigilance plans for ZIKV vaccines to help generate the best possible evidence on the safety and efficacy of these vaccines in pregnancy.

In some cases, regulatory authorities can request or require that sponsors conduct Phase IV studies. For instance, the US FDA can require sponsors to conduct additional

⁸ The ethics of conducting a Phase IV placebo-controlled RCT of a ZIKV vaccine in pregnancy will depend on a variety of considerations, including the nature of the recommendation for use of the product in pregnancy (e.g., routine, only in an outbreak, not yet recommended due to insufficient evidence) and the background risk of ZIKV infection, among others.

post-approval studies or trials for products approved under the accelerated approval pathway to further demonstrate clinical benefit. They can also require post-market assessments of risk signals or known serious risks associated with a product (149). Similarly, the European Medicines Agency, has a variety of post-authorization measures that can be requested or required (152). These include specific obligations that can be imposed for products approved with conditional marketing authorizations, a pathway potentially available in emergency situations (153). Where possible, these and other regulatory requirements should be leveraged to support development of an adequate evidence base for ZIKV vaccines in pregnancy.

Although generally not as informative as well-designed and properly executed prospective observational studies, surveillance systems can provide valuable information. Both the US and the EU have mandatory requirements for passive reporting of any adverse events potentially associated with immunization, captured in the Vaccine Adverse Event Reporting System (VAERS) and EudraVigilance systems, respectively. These and other adverse event reporting systems, such as the Vaccines and Medications in Pregnancy Surveillance System and Vaccine Safety Datalink, can serve as important mechanisms to identify safety signals for vaccination in pregnancy that require further study (154). Additionally, US FDA oversees an active safety surveillance system for vaccines called the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program. PRISM program leaders have already identified vaccine safety in pregnancy as well as immunization in pandemic responses as major concentrations for inquiry (155). PRISM and other active surveillance systems may serve as critical tools to further build the evidence base and safety profile for ZIKV vaccines in pregnancy. The example of PRISM also highlights the potential benefits of strengthening health information systems and how growing use of electronic medical records can enhance post-marketing studies—including those focused on safety in pregnancy. (Recommendation 10 provides additional support for improving health information systems to strengthen safety assessments through the establishment of baseline rates of adverse pregnancy and birth outcomes.)

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.

Many ZIKV vaccines under development use replication-competent platforms with theoretical risks to the fetus or novel platforms with limited or no pregnancy-specific safety data (20,21). While they may not be developed with the expectation of use in pregnant women, many if not all these candidates will be targeted to women of childbearing potential (WOCBP) and trials will include WOCBP among their participants. It is inevitable that some WOCBP will unknowingly be pregnant at the time of vaccine administration or will become pregnant within a clinically relevant period following vaccine administration. Pregnancy-risk characterization and mitigation will be needed for WOCBP who may be inadvertently exposed in trials as well as in post-licensure or emergency use vaccination campaigns.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) endorses the timely conduct of reproductive and developmental toxicology when enrolling WOCBP in trials. The ICH calls for reproductive toxicology studies to be completed ahead of inclusion of WOCBP in trials, though it allows for certain exceptions on the bases of “knowledge of the mechanism of action of the agent, the type of pharmaceutical agent, and the extent of fetal exposure or the difficulty of conducting developmental toxicity studies in an appropriate animal model” (156). When reproductive toxicology studies would provide useful safety signals on vaccine platforms with limited experience in pregnancy, they should be collected earlier in the clinical development plan than the current practice in R&D, and ideally ahead of regulatory approval. As we noted previously, evidence of safety in pregnancy may be important to public health and other decision-makers responsible for selecting which vaccine to deploy in outbreak responses and prevention programs, where significant numbers of unintentional exposures of pregnant women can be anticipated.

While reproductive toxicology data can be useful, animal models—which are informative only to a point and can be misleading—are no substitute for information that can be obtained from women and their offspring. Those developing ZIKV vaccines should develop and implement well-designed plans to capture valuable data on maternal, fetal, infant, and child endpoints from inadvertent vaccination of pregnant women during the course of the trial. Historically, data from inadvertent exposures has been a key source of information regarding the safety of vaccines in pregnancy, but has been limited (109).

One challenge to drawing appropriate inferences from inadvertently exposed pregnant women in ZIKV vaccine trials is the possibility that these trial participants may also have been exposed to wild type ZIKV or other agents capable of producing adverse outcomes that could be falsely attributed to the vaccine. Data collection plans should include appropriate screening for other possible causes of fetal, infant, and child harms in order to avoid flawed attribution of harms to a vaccine that is actually safe to use in pregnancy. Other hallmarks of a well-designed plan are the prospective identification of exposures before neonatal outcomes are known and the testing for relevant correlates of immunity used in the study to determine level of protection from vaccine administration. This last point will have particular relevance to both the individuals exposed in a trial who need to know if they are protected against ZIKV, as well as broader implications for the class of women who may be exposed in pregnancy in future vaccination campaigns.

Preferably, systematic observational studies of inadvertent pregnancy exposures in vaccine trials should also entail longitudinal evaluation of immunogenicity over time to assess the potential for conferred immunity and durability of protective immunity for future pregnancies; immunogenicity among neonates exposed in utero (cord blood at minimum); longer-term follow up among children (3–5 years) exposed in utero to replication-competent candidates to assess for the potential of vaccine-associated CZS; and maternal viremia and viral shedding among women exposed to replication-competent ZIKV vaccines.

To note, observational studies on pregnant women inadvertently exposed to a ZIKV vaccine candidate will likely capture data earlier in gestation than may be possible in a trial prospectively enrolling pregnant women. This underscores the need to ensure interpretation of all pregnancy-specific data is informed by the gestational age at which exposure occurred to appropriately account for the dynamic state of pregnancy and the variability in potential risks and immunological response across the pregnancy. For instance, up to a third of early pregnancies end in miscarriage (157), so misattribution of a ‘natural’ loss to early vaccination is likely. All highlight the importance of careful design, prospective data collection, and interpretation of study results in the context of the best available data on background rates of pregnancy-specific outcomes.

Observational studies of women participating in trials who are inadvertently exposed to a vaccine while pregnant should include not only women who are pregnant at the time of vaccine administration but also women who become pregnant shortly after administration (periconception) within a relevant window of time in which the vaccine candidate's mechanisms of action may be actively working to produce immune response. Data from these women will be important for informing WOCBP how long they should wait after vaccination before becoming pregnant as well as provide information to inform choices when pregnancy does occur just after immunization.

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 vaccine 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.



We do not yet know which ZIKV vaccine candidates will prove successful and be authorized for use in clinical settings and public health programs. However, based on the current pipeline, some subset of ZIKV vaccines under development that become approved for use may not be deemed acceptable for use in pregnancy. Because we can reasonably expect that ZIKV immunization efforts targeting WOCBP will result in sizable numbers of inadvertent vaccine administrations in pregnant women, the research and public health communities have a responsibility to pursue evidence that will allow for the best possible counseling on the implications of these exposures. Recommendation 6 calls for early efforts to collect data from inadvertent exposures in the context of trials, ahead of any use authorizations. Yet, we know that information from inadvertent exposures in trials will be limited, and more work will need to be conducted to better characterize the potential risks of administration in pregnancy.

For vaccines not intended for use in pregnancy, the greatest source of data will likely come from inadvertent exposures once the vaccine is rolled out for use. Therefore, it is critical that mechanisms be in place to systematically capture and analyze data on relevant maternal, fetal, and child indicators and outcomes of safety and immunogenicity. Many of

the surveillance programs used to monitor intentional vaccine administrations in pregnancy (some identified under Recommendation 5) can also be leveraged to capture data from unintentional exposures. Also, in recent years, there has been increased focus on the systematic surveillance for adverse events following immunization (AEFI) for pregnant women and their offspring (151,158–160). A recent global survey identified 11 active surveillance systems across countries in various income brackets and geographic regions to detect serious AEFI in pregnant women or their infants, with 4 of these systems specifically focused on inadvertent vaccine administrations in pregnancy (159). The survey also identified opportunities to better leverage passive surveillance systems by adding more targeted questions about pregnancy status and relevant outcomes to their surveillance forms.

Alongside calls and efforts to strengthen the active and passive surveillance systems for AEFI, significant efforts have been underway to developing consistent definitions and standards of reporting on any vaccine associated adverse events when administration occurs in pregnancy (151,160). The Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project has developed several guidance documents to improve data collection and advance the evidence base on maternal, fetal, and neonatal outcomes in support of the global agenda for vaccination in pregnancy. This includes a consensus list of terms and concept definitions of key events for monitoring immunization in pregnancy, along with recommendations and immediate actions to further strengthen monitoring of programs in which pregnant women will receive vaccines (161). Ahead of rolling out ZIKV vaccines, these standard forms to capture AEFI should be revisited and updated to reflect any additional outcomes of interest that emerge specific to ZIKV vaccines and the nature of the pathogen. This will be particularly important to address concerns about the theoretical risk that replication-competent ZIKV vaccines could result in vaccine-associated CZS. Standard case definitions for CZS and robust surveillance efforts early in the rollout of replication-competent ZIKV vaccines can critically inform what, if any, risks are associated with receiving these vaccines in pregnancy and how these exposures should be clinically managed.

FIGURE 1 | SUMMARY OF RECOMMENDATIONS AIMED AT DATA COLLECTION EFFORTS, BY VACCINE CATEGORY AND AUTHORIZATION STATUS

	Pre-Authorization	Post-Authorization
	<p><i>Vaccines anticipated to be acceptable for use in pregnancy</i></p> <p>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.</p>	<p><i>Vaccines deemed acceptable for use in pregnancy</i></p> <p>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.</p>
	<p><i>Vaccines not anticipated to be acceptable for use in pregnancy, but targeted to WOCBP</i></p> <p>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.</p>	<p><i>Vaccines not deemed acceptable for use in pregnancy at the time of authorization</i></p> <p>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.</p>

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.

Experts in obstetrics and gynecology, maternal–fetal medicine, pediatrics, neonatology, and pediatric neurology, especially those who have experience with ZIKV and CZS, have specialized knowledge that is critical to properly identifying and addressing the needs and interests of pregnant women and their offspring. Their involvement in the design of clinical trials and other data gathering activities will help ensure that decisions about the inclusion or continued participation of pregnant women are based on the most informed understanding of the comparative risk and prospect for benefit to pregnant women and their offspring of participation and non-participation.

The involvement of these experts in the design and interpretation of clinical trials and observational studies, as well as registries and other forms of data collection, will also

strengthen the validity of these evidence generating activities by ensuring the identification of appropriate endpoints and the interpretation of findings in terms or parameters of normalcy for pregnant women, newborns, and children. For example, maternal health experts are particularly attuned to the ways that pregnancy is a dynamic state that causes significant physiological changes across gestation, while child health experts may be particularly attuned to the implications for data interpretation of development changes in offspring, both pre- and post-birth.

The historical reliance on post-market data from registries to assess vaccines in pregnancy has highlighted a number of potential shortcomings of this strategy, including the bias toward reporting of adverse events without a denominator for the total number of vaccine exposures or complete reporting of other potential causes for adverse outcomes. This can lead to an over-estimation of attributable risk to certain vaccines in pregnancy, without corresponding consideration of the potential benefits derived from immunizing against vaccine-preventable illness in pregnancy. Including experts in maternal and child health in design and evaluation can lead to improved data collection and more useful and clinically relevant findings.

Various expert groups, such as the GAIA network, have already developed consensus guidance and sample protocols on important aspects of trial design and adverse event reporting (126). Experts in maternal and child health, particularly those with experience with CZS, are needed to further adapt and contextualize this material for ZIKV vaccine research. A recent paper on science preparedness for pregnant women during public health emergencies called for the establishment of “a network of experts in obstetrics and pediatrics research” that could be called upon in the event of a public health emergency in which considerations of pregnancy are central (such as ZIKV) to inform development, evaluation, implementation, and analysis of trials (162).

Pregnant women deserve that decisions affecting them will be made in careful, thoughtful, and evidence-based ways, involving the most informed experts possible. Additionally, should a vaccine be recommended for use in pregnant women, providers of reproductive and sexual health services, such as obstetricians/gynecologists, midwives, and other women’s health practitioners, will likely be an important group deploying ZIKV vaccines. In order to enhance buy-in among these providers during vaccine roll out, it is critical to involve them throughout the ZIKV vaccine development process.

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.

Community engagement and participatory-based approaches to biomedical research have been increasingly recognized as good practice in the design and conduct of clinical trials and human subjects research (40,163,164). Early and ongoing engagement with communities and sub-groups that will be involved in or affected by research studies not only offer a way to demonstrate respect for these groups, but can also help improve the design of research studies (40,163,164). In the case of ZIKV vaccines, pregnant women are key stakeholders whose interests are central to the development and future deployment of all ZIKV vaccine products targeted to WOCBP.

In the context of ZIKV vaccine trials enrolling pregnant women, soliciting the perspectives of pregnant women from the community can be important to various aspects of trial design, including what information and outcomes are most important to pregnant women, culturally relevant considerations for the consent process, and appropriate frequency and location of study visits based on the daily demands on their lives throughout pregnancy and after delivery.

As has proven to be the case in other vaccine contexts, these engagement activities could provide clarity about the kinds of information pregnant women would need to consider taking part in a ZIKV vaccine trial (165). Similarly, these insights can critically inform the design of long-term follow-up and prospective observational studies. Research groups that have successfully conducted studies with pregnant women for other diseases and interventions have recognized the value and importance of engaging with the community to inform them about the study aims, address common misconceptions, improve recruitment and retention of participants, and address cultural and logistical barriers to participation (139,166).

The perspectives of pregnant women will also be important to inform ZIKV vaccine trials with WOCBP that are not enrolling pregnant women. Involving pregnant women in engagement activities for these trials can provide critical insights for how best to prepare for the inevitable instances when women participating become pregnant during trials.

Engagement with pregnant women can help researchers develop plans to effectively communicate information and available options to women who become pregnant during trials. In some instances, these women will be offered the option to finish the vaccine schedule through a re-consent process or to enroll in a parallel observational study. Similar to the trials prospectively enrolling pregnant women, these protocols should take into account the perspectives, attitudes, and experiences of the types of women who may continue participating in some type of study after becoming aware of a pregnancy.

A number of resources and guidance exist for how to do community engagement for biomedical research trials and there are various approaches to participatory-based research (40,164). In some cases this may mean involvement of pregnant women in existing engagement platforms like community advisory boards. In other instances it may entail more dedicated formative research or early engagement focusing on pregnant women. The important point to underscore is that the interests of pregnant women and their offspring should be adequately represented in engagement activities done in support of ZIKV vaccine trials.

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.

When assessing the safety of any new vaccine, it is critical to have reliable data on the background rates of possible adverse outcomes that could be associated with the vaccine (167). This includes background rates of adverse pregnancy and birth outcomes, such as miscarriage, stillbirths, low birthweight or preterm birth, and congenital malformations—particularly when vaccines will be administered in pregnancy (167,168). These data on background rates are necessary to determine whether adverse outcomes that occur around the time vaccines are administered represent legitimate safety concerns or whether they are consistent with typical rates of such adverse events and unrelated to vaccine use. The need for reliable background rates applies both in the context of trials as well as in ongoing observational studies and surveillance to monitor safety after a product is authorized for use. These data are a crucial baseline to inform safety assessments of ZIKV vaccine use in

pregnancy and help characterize what if any risks to the woman or future offspring are in fact are a matter of concern when using the vaccine during pregnancy. Additionally, information on background rates of adverse pregnancy and birth outcomes are essential for responsibly communicating potential risks and benefits of ZIKV vaccines to the public and, where appropriate, reassuring the public to instill confidence in the safe and effective use of these critical public health tools (see Recommendation 11).

It is worth underscoring the importance of collecting locally relevant, population-based background rates in areas where ZIKV vaccine trials will be conducted and in areas where ZIKV vaccines are likely to be deployed as part of public health programs. The rates of adverse outcomes such as preterm labor, stillbirth, and congenital malformations can vary widely by geographic region, ethnicity, age, season, and other factors (167,168). It is not too early for the areas most likely to have future ZIKV outbreaks—such as those identified by the WHO that already have documented cases of local transmission and/or competent vectors—to begin investing in studies to track background rates of adverse pregnancy outcomes alongside their surveillance efforts (18).

We recognize that there are many challenges to establishing reliable sources of information documenting background rates of adverse pregnancy and birth outcomes—particularly miscarriages that occur early in pregnancy and often go unnoticed, unreported or underreported. At the same time, there are opportunities to leverage, strengthen, and build upon existing data sources and health information systems to establish locally relevant background rates. For instance, various countries conduct routine Demographic and Health Surveys (DHS) and Multiple Indicator Cluster Surveys (MICS), which include certain maternal and neonatal indicators. Other large-scale programs targeted to reproductive, maternal, newborn, and child health collect massive amounts of local and regional data on maternal and newborn outcomes for research purposes as well as to monitor and evaluate the progress and impact of their programs. Additionally, there may be rich data to be drawn from the large cohort studies conducted in many countries affected by the most recent waves of ZIKV across Latin America, through which many infants born with congenital defects were tested to determine if such malformations were attributable to ZIKV infection or other causes. These studies and simultaneous efforts to strengthen health information systems can and should be leveraged to provide critical information on background rates, which will not only inform safety assessments for ZIKV vaccines and other maternal immunizations, but also contribute to the broader agenda to improve maternal, newborn, and child health.

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.

As noted above, there is a historical tendency toward risk distortion when it comes to potential adverse outcomes in pregnancy (169). The misinterpretations and inflations of associated harms with biomedical products can lead to pregnant women not using biomedical interventions that would actually provide net benefits to them and their offspring. In the context of ZIKV vaccines, because congenital harm is the greatest fear, these distortions maybe particularly pronounced unless great care is taken to communicate appropriately.

As discussed in Recommendation 10, one best practice for communicating pregnancy-specific ZIKV vaccine findings is to ensure that any reports of adverse pregnancy or birth outcomes occurring in studies are interpreted and presented in comparison to the background rates of negative pregnancy or birth outcomes in the general population. Because many people are not aware of the background rates of miscarriage in early pregnancy or the frequency of adverse birth outcomes, providing this information can help contextualize these findings and convey whether the vaccine is associated with any additional risks beyond those occurring in a typical pregnancy. It is also important that any risks associated with a ZIKV vaccine be presented alongside the likely benefits of vaccination to avoid solely focusing on small probabilities of harm amidst high likelihood of clinical benefit.

Engaging the media in this role of responsible communication will be critical. For instance, in 2009 when H1N1 influenza was causing significant morbidity and mortality among pregnant women in the US and campaigns were underway to vaccinate pregnant women against the virus, the National Vaccine Program Office (NVPO) conducted a series of “table-top” sessions with journalists from various local and national newspaper outlets (170). The purpose of these meetings was to educate reporters on baseline rates of miscarriage in the population in the hopes of mitigating sensationalist stories falsely attributing miscarriages to H1N1 vaccines, and the NVPO felt that these efforts were largely successful in that endeavor. The role of the media in spreading information, or misinformation, cannot be understated. The rise of ZIKV in Brazil was accompanied by

rampant rumors and conspiracy theories, with the spread of misleading information through social media dominating posts shared about the disease (171,172).

Information directed to potential recipients of a vaccine, including on labels, patient package inserts, or consent forms, represents another important mode of communication of study-related data on use in pregnancy, with significant influences on adoption and uptake among pregnant women (173). Typically, labelling and vaccine product information for maternal immunizations have been guarded and negative in tone, particularly in the absence of reliable safety data (174). It has been acknowledged by experts in vaccine research and global health that labels containing statements about use in pregnancy like “administer with caution” or “if clearly needed” or “your doctor needs to assess the benefits and potential risks of giving you the vaccine if you are pregnant” are not useful and often lead to misperceptions and sub-optimal uptake of recommended maternal immunizations (173).

In recent years, there have been moves by the EMA, FDA, and Health Canada to ensure more nuanced and structured information about safety and efficacy (175,176). This includes providing more comprehensive information on what pregnancy-specific data exist and from what sources of evidence, as well as inclusion of statements on background rates of pregnancy loss. For ZIKV vaccines, communicating the fuller range of evidence generated on ZIKV vaccine products through various data collection activities will be imperative to ensure providers and policymakers have appropriate information to inform clinical and public health decisions. Experience with existing maternal immunizations suggests that the information on a product label can influence policymakers’ decisions to adopt a vaccine as part of a national program or response (80).

Lastly, in line with ethical practice in the conduct of any research study, ZIKV vaccine investigators should communicate and engage with local members of study communities early and often. When endeavoring to engage the study community and report back on findings of study activities, research teams should be cognizant of approaches to responsibly convey findings relevant to pregnancy in ways that are accessible and contextualized by background rates of adverse outcomes as well as local fears and misperceptions surrounding ZIKV and ZIKV vaccines.

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.

BOX 9 | FAIR ACCESS

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 be permitted to authorize or decline participation on their own.

We now turn our attention from pregnant women, as a class, to individual pregnant women and why they, as individuals entitled to equal respect and fair treatment, should have fair access to participate in ZIKV vaccine trials that involve the prospect of direct benefit.

Rationale

As discussed in the background section, the principle of fair access to research involving the prospect of direct benefit is a key and independent pillar of research ethics (see Box 2). Any research involving the prospect of direct benefit must meet standards of fair inclusion, in which those who could benefit from inclusion, and who otherwise meet general criteria of scientific relevance and regulatory protection, should be afforded the opportunity to enroll. This applies to pregnant women no less than to other potential research subjects. Indeed, with pregnant women, the benefits of trial participation may be especially high, as benefits may accrue to two entities, the woman and her future child.

This principle has important implications for ZIKV vaccine efficacy trials conducted in communities with ongoing ZIKV infection. Pregnant women at risk of ZIKV infection are clearly among those with the potential to benefit significantly from participation in these trials. Indeed, compared to other women of childbearing potential, women already pregnant are among those with the most to gain. Women of childbearing potential who are not yet pregnant are likely to be provided contraception, reducing their risk of pregnancy and, with it, of bearing a child with CZS. Women who are currently pregnant are beyond that layer of protection; access to a potentially efficacious vaccine may be one of the few modes of protecting the fetus from infection, especially in areas of low access to vector control. Further, some studies suggest that pregnant women are less likely to use condoms

because there is no longer a contraceptive motive, so may be at greater risk of sexual transmission of ZIKV than their non-pregnant counterparts (177,178).

For ZIKV efficacy trials, as for any trial offering the prospect of direct benefit, it is unethical to presumptively exclude pregnant women from participation. Instead, decisions of inclusion/exclusion must be based on specific determinations of the potential benefits of participation and of research-related risks. Further, fair access to the prospect of direct benefit requires that the pregnant woman alone be the locus for authorizing or declining enrollment.

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.

In the case of ZIKV vaccine trials, as with trials generally, fair access requires that pregnant women should be eligible for prospective enrollment whenever the potential benefits of participation are reasonably favorable compared to the research-related risks (179). As with other research involving pregnant women, this means careful appraisal of preliminary and accruing evidence on risks and potential benefits to both women and their offspring.

Consideration of potential benefits entails assessment of the background rates of ZIKV transmission in the study area and risks of exposure, the best available evidence on the likelihood that ZIKV infection at different points in gestation will result in adverse outcomes, and existing data on the potential for the vaccine candidate to induce immunological protection in the general population. Although immunogenicity data specific to pregnancy would be helpful, these data are likely not necessary to determine prospect of direct benefit. In most cases, promising immunogenic responses in non-pregnant adults would be sufficient to assess the prospect of direct benefit of trial participation for pregnant women.

Consideration of risks includes assessing available evidence on the safety of the vaccine platform and adjuvant in pregnancy, any data from preclinical studies about the candidate's safety in pregnancy, and any other specific biologically plausible risks of a given platform or candidate.

For all of these risk-benefit assessments, it is worth emphasizing, again, that decisions about fair access and eligibility must be approached as comparatively weighing any risks

potentially associated with the investigational vaccine against the risk of being denied the prospect of protection from wild type ZIKV. Critical to these assessments are the baseline risks faced by the woman and her offspring if the woman remains unvaccinated during the period of the trial. This requires consideration of the likelihood of wild type infection, including specifics, if available, about the immediate context (for instance, whether ZIKV has become endemic in the region), the social context including access to other prevention and treatment measures, and the severity of impact from infection.

Trials of vaccine candidates that employ platforms and adjuvants with a long history of fetal safety (i.e., non-replicating platforms such as inactivated whole and subunit platforms that use an adjuvant with a strong safety profile in pregnancy such as alum) are the most immediate and obvious ZIKV vaccine trials that, on the risk side, are likely to meet the fair access criterion. In addition to the existing track-record, they pose no biologically plausible threat of infecting the fetus with replication-competent viral vaccine. Neither cohort studies nor the Vaccine Adverse Event Supporting System have found any significant increase in adverse maternal or infant outcomes among vaccinated pregnant women for inactivated influenza vaccine (180). According to ACOG and the US Advisory Committee on Immunization Practices (ACIP), “there is no evidence of adverse fetal effects from vaccinating pregnant women with an inactivated virus or bacterial vaccines or toxoids, and a growing body of robust data demonstrates safety of such use” (181). Against the backdrop of our evolving scientific understanding of ZIKV pathophysiology, non-replicating vaccines could offer significant prospect of direct benefit to pregnant women and their offspring in areas at risk of locally-acquired infection. With reassuring evidence on the safety profiles of these vaccine candidates—including the absence of safety signals of reactogenicity such as high fevers—it is reasonable to conclude that where there is a plausible risk of locally-acquired ZIKV infection the potential research-related benefits to pregnant women and their offspring of trial participation would outweigh the risks. Under these circumstances, it would be unfair to exclude pregnant women from enrolling in Phase II–III trials.

More challenging questions of prospective enrollment of pregnant women arise in efficacy trials involving platforms and adjuvants not yet used during pregnancy. For instance, novel mRNA and DNA ZIKV vaccines have been among the first to advance into Phase I and II trials. These nucleic acid platforms do not pose the threat of replicating ZIKV, but they lack preexisting data on use in pregnancy, and potential associated risks are unknown. As research continues, and understanding of potential risks and benefits of DNA and mRNA ZIKV vaccine in pregnancy grows, there may be an increasingly compelling case for including pregnant women in Phase II-III efficacy trials for these candidates. Another platform not widely used in pregnancy is live attenuated viral vaccines. In contrast to novel

platforms, we do have decades of experience of inadvertent and intentional use (e.g., yellow fever) of live vaccines in pregnant women, and data collected have been reassuring (109,182–184). Yet there is a longstanding backdrop of theoretical concern, and live attenuated vaccines for ZIKV raise a more specific consideration given the biological plausibility that introducing a weakened but replication-competent virus in pregnancy could result in some of the exact adverse CZS outcomes that the vaccine seeks to prevent. At this time we believe it unlikely that the ZIKV context would support prospective enrollment of pregnant women in live ZIKV vaccine trials, though analysis of inadvertent exposure data may at some point shift the calculus. That said, it is critical that, as our understanding of ZIKV and its outbreaks continues to unfold, and evidence grows about vaccine platforms relevant to fetal safety, the research and public health communities stay agile and revisit the question.

Because of the critical role that ethics oversight entities play in protecting against unfairness, it is important they remain vigilant for instances in which pregnant women are being wrongly denied access to the potential benefits of participating in a ZIKV vaccine trial. For example, if protocols for ZIKV vaccine efficacy trials of candidates anticipated to be acceptable for use in pregnant women are submitted without a provision for inclusion of pregnant women, oversight committees should require justification of why they are being excluded. Oversight committees are encouraged to work collaboratively with researchers to identify trial designs that will work with pregnant women.

As noted in Recommendation 7, it is advisable that research ethics committees reviewing ZIKV vaccine protocols include or consult relevant experts in maternal, fetal, and infant health when making determinations about eligibility for pregnant women. Such expertise is important to accurately assess risks and potential benefits, including background risks of pregnancy and infant development, and determine if the prospective benefits offered by the study will outweigh the risks in different contexts, including during active outbreaks.

When trials are conducted in areas where there is significant risk of ZIKV infection, it may be ethically problematic to randomize pregnant women to a placebo arm of a trial. Their situation is relevantly different from those of women in the trial who are likely not pregnant and who should be counseled about the risks of CZS and offered contraception. Women who are currently pregnant are beyond that layer of protection. Depending on the risk of infection (based on the background rate of infection and women's realistic access to means of decreasing personal exposure to mosquitoes), there may be cases in which it is appropriate to shift pregnant women to a non-randomized trial design.

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.

In trials enrolling women of child-bearing potential, including ZIKV vaccine trials, it is predictable that some women not known to be pregnant at the time of enrollment will discover a pregnancy after enrollment, even where contraception is advised or provided (123,185). In anticipation of that scenario, it is critical that all ZIKV vaccine trials have a plan to respond when a participant becomes pregnant and has an unintended exposure to the study-immunizing agent. This plan should include asking women who become pregnant while on trial to participate in a long-term follow up study, as described in Recommendation 4. This follow-up study should offer ancillary benefits comparable to those offered in the larger trial (see Recommendation 14). Further, this plan needs to address additional considerations in trials of ZIKV vaccines with multiple doses.

If the pregnancy occurs after the vaccine schedule has begun but before it is complete and likely able to stimulate adequate immune response, a determination must be made about whether the woman should be permitted to receive additional doses. It is critical that the acceptability of finishing the schedule depend on a careful risk-benefit assessment made relative to the particular risk and potential benefit to the specific individual woman and her fetus, rather than historical patterns of presumptive discontinuation. Further, those making the determination must bear in mind that there are ethical reasons, not just reasons of scientific interest, that must be considered in assessing whether to allow a pregnant woman to finish a vaccine schedule. When enrollment takes place in ZIKV-threatened areas, it is critical that women who have volunteered to participate, hoping for protection and now faced with the very situation in which protection matters most, not be summarily sent off protocol. Instead, determination of eligibility to continue should be based on a specific risk-benefit analysis focused on the pregnant woman and her future child.

For vaccine trials where pregnant women are permitted to prospectively enroll, it should be straightforward to allow women participants who become pregnant after enrollment but before the scheduled dosing begins or has finished to continue to receive vaccine doses.

That said, such trials should still include a robust re-consent process to cover issues not explicitly addressed in the consent process prior to pregnancy.

In trials for which pregnant women are not appropriately eligible for prospective enrollment, the determination about continued dosing is complex. In these instances, it will be critical to assess and weigh the potential benefits and harms based on the characteristics of the vaccine, the circumstances of the pregnant participant, and the maternal–fetal risks and benefits specific to that individual case, including possible risks of antibody enhancement associated with receiving an incomplete vaccination series. In both types of trial, the core moral point is that it is unacceptable to deny pregnant women the potential benefits of trial participation without a specific and compelling justification.

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.

Women who become aware of a pregnancy while participating in a ZIKV vaccine trial, whether they choose or are permitted to continue completion of the vaccine schedule, should be provided all study-related benefits and ancillary care to which they would otherwise be entitled if they continue to come for non-interventional follow-up. These study-related benefits are owed not only because these women will likely continue on as participants in a parallel observational study to gather important follow-up data, but also as a matter of reciprocity for the contribution they had already given by volunteering in the original vaccine study (186). In addition, continued access to study-related benefits may help allay the distinctive fears and anxieties surrounding risk of ZIKV infection in pregnancy. Women who become pregnant in the context of a trial now more acutely face the risks of adverse outcomes that the trial intervention aims to prevent.

Research ethics committees should therefore require and researchers should ensure continued provision of study-related ancillary benefits to which women participants who become pregnant would otherwise be entitled, including any regular monitoring, financial incentives, or ancillary care benefits associated with trial participation. In addition, they and their partners should be offered support, information, and counseling. Given that a

pregnant woman is likely to have agreed to enter the trial from a desire to make sure that any future offspring will be protected by the vaccination, researchers must be cognizant of the anxiety and stress that a woman will experience in finding out that she is pregnant and facing precisely the risk that likely motivated study participation, only to be expelled from the study. Further, to the extent that other preventive measures (e.g., condoms, mosquito nets) are made available through the study, the pregnant woman, who is now at confirmed risk of having a child with CZS, should not lose access to these benefits.

Women participants who become pregnant before receiving or completing the trial's vaccine schedule, and who decline or are ineligible to continue receiving the study intervention, should be offered the opportunity to receive or complete vaccine dose(s), postpartum. For women who are lactating, this opportunity would be conditional on an assessment that the prospect of benefit to the woman, her newborn, and subsequent offspring outweighs the risks. Access to a ZIKV vaccine through the trial is valuable because of the likelihood of subsequent pregnancies and because some trial participants may not otherwise have regular contact with healthcare facilities or clinicians.

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.

Fair access also requires that when pregnant women 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, be required.

Pregnant women are the moral equal of other self-governing adults. CIOMS, PAHO, and Subpart B are clear that pregnancy is no exception to the principle that competent adults be the locus of consent for trials that offer the potential to benefit them. The CIOMS guidelines state that the pregnant woman alone "is the one to make the final decision about the acceptability of these risks to her and her fetus or infant" in all research scenarios (40). Subpart B of US federal human subjects regulations defends one exception to this general commitment (70). For research that holds out the prospect of direct benefit solely to the fetus, offering no possible clinical benefit to the woman, it requires the father's additional consent for the pregnant woman to participate in the research (with exceptions for the father's unavailability or in cases of pregnancy resulting from rape) (70). This provision has been strongly criticized as disrespectful to women and often unworkable in

practice (67,69). Regardless, the provision is not at issue in the case of ZIKV vaccine trials, since vaccination also offers the prospect of direct medical benefit to the pregnant woman from her own risks from ZIKV infection. Whether or not the prospect of direct medical benefit to the future child is greater, the fact of the woman's own prospective benefit makes the case clear even for those who concur with Subpart B's approach.

Researchers should support pregnant women who wish to involve partners, family members, and other personal supports in the decision to join or remain in ZIKV vaccine trials. It is important for community trust that fathers and other partners are given the opportunity to engage with and learn about the trial. That said, at the end of the day her consent, and hers alone, should be dispositive. No one else's consent can substitute for the woman, and no one else's consent should be a further requirement, since it can limit her fair access to a trial that she may believe is best for her and her offspring. When pregnant women are otherwise eligible to participate in clinical research, the only requirement for enrollment should be the informed consent of the pregnant woman.

As the age of consent for research participation is jurisdiction-specific, researchers should consult local legal experts to determine the specific age for sole authorization for their study locations. Additionally, informed consent procedures should convey to women what the local policies are with regard to pregnancy termination. For trials enrolling pregnant women prospectively, the potential vaccine-associated risks to offspring are in many cases likely to be extremely low. Nonetheless, because participating in a trial may increase the likelihood that pregnant women will become aware of abnormalities in fetal development from any cause, it will be important to inform women about what their legally available options are for terminating pregnancies prior to enrollment.

APPENDIX A: WORKING GROUP MEMBERS

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Clinical Research and Development Manager in the Division of Clinical Trials and Pharmacovigilance, Butantan Institute.

APPENDIX B: CONSULTATION STRATEGY

From April 2016–April 2017 we engaged in a broad consultation strategy to cohere with our engagement-driven approach to guidance development and ensure our guidance was informed by relevant experts and the most up-to-date information on the evolving ZIKV crisis. The consultations had two primary objectives: (1) fact-finding and scoping on ZIKV pathophysiology, epidemiology, vaccine development, and potential strategies for public health rollout with an efficacious vaccine; and (2) soliciting feedback and perspectives on whether, when, how, and why pregnant women should be included in various ZIKV vaccine R&D activities for different types of candidate vaccines. To include broad and diverse participation among key stakeholder groups, we purposively targeted experts from a variety of organizations, including: global and national public health agencies and regulatory authorities; public and private research institutions; pharmaceutical companies; public and private funders; medical associations specific to obstetrics and maternal–fetal medicine; and non-profit NGOs working on maternal child health and/or emergency response efforts (see Fig. B.1).

FIGURE B.1 | ORGANIZATIONAL AFFILIATIONS OF CONSULTED EXPERTS



In total, we spoke with 61 different experts with a wide range of expertise (See Fig. B.2). Some of these experts were invited to join our Working Group. Most consultations were conducted over the phone or in-person with one or two experts present. We also conducted one medium-sized group consultation with five participating content experts.

FIGURE B.2 | AREAS OF EXPERTISE REPRESENTED

Areas of Expertise Represented*	
Bioethics	15
Vaccine science, development, and trial design	11
Maternal fetal medicine, obstetrics and gynecology, or maternal immunization	13
Pediatrics	3
Pharmaceutical company representatives	7
Public health policy or vaccination implementation strategy (any macro level expertise)	14
Regulation	11
Total Number of Consultations Conducted	42
Total Number of Experts Consulted	61

* Totals from these categories exceed the number of people consulted, since some people we consulted have expertise in multiple areas and are counted as such.

Additionally, we conducted a larger one-day in-person consultation session in November 2016 as a satellite meeting of the Global Forum on Bioethics and Research in Buenos Aires, Argentina. This meeting included 25 participants with two facilitators and one note-taker. The meeting agenda and participant list is included in Appendix C.

APPENDIX C: GFBR SATELLITE CONSULTATION MEETING

MEETING PARTICIPANTS

Dr. Derrick Aarons

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Anis—Instituto de Bioética, Brazil

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University of Botswana, Botswana

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Oxford University, United Kingdom

Ms. Katherine Littler

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Ms. Marisha Wickremsinhe (*Note-taker*)

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MEETING AGENDA



Pregnancy, Research, and
Public Health Emergencies
ZIKA AND BEYOND

Ethical Inclusion of Pregnant Women in the Zika Vaccine Research Agenda

2 November 2016, 8:30 AM to 5:30 PM
Alvear Palace Hotel, Régence room (main floor)
Avda. Alvear 1891 (C1129AAA) Buenos Aires, Argentina

Schedule

8:30 AM – 9:00 AM	Arrival and breakfast
9:00 AM – 9:15 AM	Welcome remarks
9:15 AM – 9:30 AM	Objectives and framing of the day's discussions
9:30 AM – 10:00 AM	Briefing: Zika virus and the state of the crisis
10:00 AM – 10:30 AM	Briefing: Maternal immunization and the Zika virus vaccine pipeline
10:30 AM – 10:45 AM	Break
10:45 AM – 11:45 AM	Discussion: "Should special priority be given to development of vaccine candidates using platforms considered safe for use in pregnancy?"
11:45 AM – 12:15 PM	Briefing: Ethics and research with pregnant women
12:15 PM – 1:15 PM	Lunch
1:15 PM – 2:15 PM	Discussion: "Should pregnant women be prospectively enrolled in trials of Zika virus vaccines?"
2:15 PM – 3:15 PM	Discussion: "Should pregnant women in Zika-endemic areas have expanded access to the study compounds?"
3:15 PM – 3:30 PM	Break
3:30 PM – 4:45 PM	Discussion: "For Zika virus vaccine trials that do not prospectively enroll pregnant women, what policy should be adopted for women who become or are discovered to be pregnant after enrollment?"
4:45 PM – 5:30 PM	Wrap up and conclusion

APPENDIX D: ZIKA VIRUS STATE OF THE SCIENCE AND EPIDEMIC

Zika Virus: History, Characteristics, and Pathophysiology

The Zika virus (ZIKV) is a single-stranded RNA flavivirus, closely related to dengue, Japanese encephalitis, West Nile virus, and yellow fever (1). Although ZIKV was first identified in 1947 in Uganda near the Zika forest, until recently it received little public health or biomedical attention. Infection rates in humans were low and presented with modest and self-limiting symptoms (1,4). However, since 2007 there has been an unprecedented surge in large-scale epidemics spreading across various Pacific Islands and throughout the Americas, with subsequent studies linking infection to neurological complications and severe congenital malformations. The emerging crisis and the WHO's declaration of ZIKV as a public health emergency of international concern (PHEIC) on February 1, 2016 have led to significant scientific investigation into the virus and its biological mechanisms to better understand the threat and how best to respond to it. While vector control and other preventive measures are important components of the response, development of an effective vaccine will likely offer the greatest reduction in harms caused by ZIKV outbreaks. Understanding key aspects of ZIKV—such as the clinical presentation, the effects of congenital infection, the broad range of cells that sustain damage from infection, the potential for antibody dependent enhancement, and the development of a specific serologic test for ZIKV (without cross reaction with other flaviviruses)—is a critical step towards vaccine development. The evidence base in each of these areas is continuously evolving; current research findings are summarized here.

Clinical Presentation. ZIKV infections among adults are generally mild, with 75–80% of individuals experiencing no noticeable symptoms. When infections are symptomatic, the most common clinical presentations include mild flu-like illness, conjunctivitis, rash, arthralgia, and joint pain (5,187). However in rarer cases, ZIKV infection has been associated with increased incidence of Guillain-Barré Syndrome (GBS) and other central nervous system complications in adults, as well as myocarditis (188–190). GBS can cause short- and long-term neuromuscular paralysis, though the pathophysiological mechanisms underlying ZIKV-associated GBS are still not well understood and require further investigation. Because of the association between ZIKV infection and GBS, as well as observations correlating elevated rates of GBS following other types of vaccinations, efforts to develop ZIKV vaccines naturally engage concerns that a vaccine candidate could potentially induce GBS. Further exploration of both the mechanisms of ZIKV-associated

GBS and careful study and surveillance to examine risks of ZIKV vaccine-associated GBS will be necessary.

The major concern, however, about ZIKV infection is the effects of infection during pregnancy. While the sudden spike in reports of microcephaly in Northeast Brazil following a ZIKV epidemic brought attention to the virus's potential to cause significant congenital harm, it has become increasingly clear that microcephaly is the "tip of the iceberg" (191). Several prospective cohort studies and numerous case studies have revealed a constellation of neurological, joint, muscular, and ocular abnormalities to be associated with ZIKV infection during pregnancy. Congenital Zika syndrome (CZS) — a condition that encompasses this range of birth defects — is clinically associated with seizures, swallowing difficulties, limited mobility, and uniquely piercing and ceaseless cries (7). ZIKV infection during pregnancy can also result in pregnancy loss (2,3). A prospective study of a cohort of pregnant women in Brazil found that the pregnancies of women with evidence of ZIKV infection were around four times more likely to result in an adverse outcome, including fetal loss and fetal abnormalities (2). Though it appears that ZIKV infection during pregnancy is most harmful during the first trimester, studies have indicated that harm from infection during pregnancy can occur regardless of gestational age. Recent data from a Brazilian cohort found that 55% of pregnancies had adverse outcomes after maternal infection in the first trimester, 52% after infection in the second trimester, and 29% after infection in the third trimester (2). Among infants born to women with confirmed recent Zika infection in the US, the recorded rates of anomalies congruent with CZS were 8% in the first trimester, 5% in the second trimester, and 4% in the third trimester (83). However, because the majority of infections are asymptomatic, the rates of CZS are not yet well determined.

Among infants born with CZS, the type and severity of conditions vary significantly and evidence is still accumulating on the range of adverse sequelae attributable to congenital ZIKV infection (7,8). Significant questions remain on the longer-term effects of congenital ZIKV infection, including among infants who appear normal at birth. In several cases, microcephaly and other symptoms consistent with CZS presentation have manifested after birth, and some research on the pathophysiology of ZIKV indicates that neurological and musculoskeletal effects, including delayed growth or development, may be expected to emerge throughout infancy and into childhood (9).

Broad Tropism. The ability of the ZIKV to infect a variety of human tissues raises a number of concerns. ZIKV is neurotropic, targeting a variety of neuronal cell types. In particular, fetal neurons, undifferentiated neurons, and partially differentiated neurons are more susceptible than mature neurons or differentiated neurons in adults. Unlike other flaviviruses, the virus is capable of infecting the placenta (as determined by evidence of

ZIKV in various placental cells) and of crossing the fetal blood-brain barrier (192,193). ZIKV has been found to be present in a variety of human fluids as well as fetal tissue cells. Case studies, as well as mouse and non-human primate models, indicate the potential affinity and persistence of the virus in ocular tissues, reproductive tissues, and various fluids including tears, sperm, urine and saliva—in some for multiple months (194–197).

Transmission. Like other flaviviruses, ZIKV is carried by *Aedes* mosquitoes and mosquito-borne transmission has been the key driver of recent ZIKV epidemics (16). However, unlike other flaviviruses, ZIKV can also be transmitted sexually with reported cases of male-to-female, male-to-male and female-to-male transmission (14,15). ZIKV can also be shed in other bodily fluids such as blood, tears, and sweat, however there is no evidence at this time that this contributes to transmission (194–197). The persistence of virus in certain fluids, including semen, raises significant concerns about the role of sexual transmission, particularly when up to 80% of infected people remain asymptomatic, as this could increase the number and duration of exposures among pregnant women even after the end of mosquito seasons (198).

Other considerations relevant to ZIKV vaccine development:

Serotype. ZIKV strains have been grouped into two lineages, African and Asian, though studies indicate that there is only one serotype. This carries implications for vaccine development—since antibodies produced in response to one strain should inhibit infection by the other, a monovalent vaccine will likely be protective against both strains (199).

Potential for flavivirus cross-reactivity and antibody dependent enhancement (ADE). The high prevalence of other flaviviruses such as dengue in areas where ZIKV is circulating complicates vaccine development processes. There is evidence suggesting that having antibodies to one dengue serotype—either from past infection or immunization—may change the clinical manifestation of disease when infected with a second dengue serotype in the future (200,201). *In vitro* studies have demonstrated that antibodies to almost any flavivirus can enhance the infection of monocytes with any other flavivirus and antibodies to dengue have been shown to enhance infection of monocytes by ZIKV. On the one hand, existing flavivirus antibodies may offer protection and help neutralize new viral infections in the body. However, there have also been *in vitro* lab studies showing the potential for antibody dependent enhancement in the context of ZIKV, which would mean that pre-existing immunity to other flaviviruses could cause more severe presentation of illness in future exposures (202). This could have implications for whether and how preexisting immunity to other endemic flaviviruses might affect manifestations of ZIKV or reactions to live attenuated ZIKV vaccines, as well as the potential for ZIKV vaccines to cause more severe illness among those exposed to dengue or chikungunya. Because the scientific

evidence on this phenomenon to-date is largely based on *in vitro* studies, the role of ADE in the ZIKV context remains unclear (202–204).

The State of the Epidemic

The first large-scale ZIKV outbreak documented in humans occurred in 2007 in the Pacific Island of Yap. Since then, outbreaks and active local transmission have been reported in at least 84 countries in the Pacific Islands, the Americas, South-East Asia, and Africa, and the WHO has identified as many as 148 countries capable of supporting future outbreaks due to the presence of competent vectors, namely the *Aedes* mosquitoes (205). One modeling study has estimated that up to 2.17 billion people live in regions conducive to ZIKV transmission (206). The increased rates of microcephaly and neurological disorders reported in Brazil following detection of circulating ZIKV led the country to declare a national public health emergency (PHE) in November of 2015. Shortly thereafter, the World Health Organization (WHO) declared ZIKV a public health emergency of international concern (PHEIC) on February 1 2016, given the rapid spread of the virus throughout the Americas and the accumulating evidence of its association with congenital harm. Although the WHO's PHEIC designation was lifted in November 2016 to signal a shift towards a longer-term strategy and some areas have seen a decline in ZIKV cases, various national PHE designations remain in place and concern alongside calls for vigilance remain high in areas with ongoing or potential future transmission.

FIGURE D.1 | MAPS OF LOCAL IDENTIFICATION OF ZIKV BY YEAR



Source: WHO



Source: WHO

Questions remain about how likely ZIKV is to persist or re-emerge in areas conducive to local transmission, with various modeling predictions about the frequency and severity of future outbreaks and epidemics. Some projections estimate current epidemics will subside within three years, with the potential to re-emerge and cause large-scale outbreaks every ten years absent an efficacious vaccine or alternative public health intervention (207). One model showed the potential for recent vector control measures aimed at reducing near-term exposures to in fact result in faster re-emergence of ZIKV with greater numbers infected, because, until there is an effective vaccine deployed, a larger proportion of the population will remain immunologically naïve and therefore susceptible to the virus in the next outbreak (30). The future patterns of ZIKV outbreaks will also depend on a range of factors, including human travel, the impact of climate change on weather supporting mosquito-borne transmission, socioeconomic factors that impact whether the built environment is more or less supportive of mosquito breeding, and the under-characterized contribution of human-to-human transmission (including sexual transmission) to localized and regional epidemics (208,209).

While the frequency and magnitude of future large-scale outbreaks are hard to predict, there is growing consensus that, following acute outbreaks in areas with local transmission, there will be sustained endemicity that may cause isolated cases and localized outbreaks for years (17). Because the virus can persist in animal reservoirs and be re-introduced to humans by mosquito vectors, it is difficult to fully eradicate the virus. This means that ZIKV will sustain the specter of fear and uncertainty for any pregnant women living in, traveling to, or having sexual partners who have visited an endemic area in the past year.

Additionally, without preventive measures and increasing human travel between countries and continents that could support ZIKV, the possibility for ZIKV to be introduced into a naïve population remains, whether or not it will lead to an epidemic. This highlights the importance of continuing to work toward development of an efficacious vaccine, even as current threat levels wax and wane in different geographic regions.

Congenital Zika Syndrome: Implications for Affected Children, Families, and Societies

The consequences of a ZIKV outbreak can be devastating, first and foremost to the children afflicted with CZS. Most vivid are cases of microcephaly, but as we learn more about the full effects of ZIKV on fetal development, further neurological and musculoskeletal effects are emerging that carry the risk of life-long deficits (7,8).

The consequences of CZS extend not only to the children born with CZS, but to their families and broader communities (10). The burden placed on women who give birth to infants with CZS is considerable; most infants born with CZS will depend on medical providers and therapists to gain function—where resources allow—and even after years of treatment or therapy, many never will. Though the most critical challenge in these situations will be to improve the health and well-being of the child, the toll that ZIKV will take on mothers, families, and communities cannot be overstated. Recent reports provide a glimpse of the challenges and burdens: a mother whose child with CZS is discharged from therapy after a year due to a lack of improvement in function; a family who walks two and a half hours to take their child to the hospital; a 14-year-old mother who fell into a deep depression following the birth of her daughter, who suffers from frequent life-threatening seizures (210). Another study followed mothers who had given birth to infants with CZS and found high levels of anxiety, depression, and psychological distress, among other indicators of low quality of life, throughout the first year following delivery (211). In addition to caring for their affected infants, these women must also navigate applications for government support, which in many cases is sparse and difficult to obtain, while managing to support other children and family members (11). Additionally, many mothers of children with CZS face social stigma and abandonment from partners and communities (12,13).

Regions where the ZIKV is currently endemic or is projected to become endemic are primarily low- and middle-income countries, often with poor public health infrastructures and a dearth of government support for children with disabilities. National government and WHO recommendations suggest delaying pregnancy to avoid the harms from ZIKV exposure, yet in many ZIKV-affected regions, there is limited or no access to reproductive healthcare or family planning, rates of unplanned pregnancy and teen pregnancy are high,

and access to abortion services is low – and in some cases criminalized (212). Additionally, many ZIKV-stricken countries are currently plagued by multiple widespread causes of increased morbidity and mortality. Disparities in the burden of disease presented by ZIKV varies not only between countries but within them as well; stratified access to healthcare, family planning, and sex education, as well as determinants of disease exposure—such as occupation, lack of air conditioning or screened windows, or autonomy to request or rely on condom use during sexual activity—will determine which populations and individuals are at highest risk for harm from a ZIKV outbreak.

The ramifications of a ZIKV outbreak on individuals and families are starkly apparent, but the impact on communities and societies more broadly will also be felt for years to come. All of the adverse sequelae from ZIKV produce conditions that will place great strain on public health infrastructures; due to the longevity of the conditions caused by CZS, this strain will endure for decades. The financial burden on the public health system will be most severe in areas where there is greatest burden of disease, which, so far in the global ZIKV epidemic, has been concentrated most in populations with low resources.

ZIKV Vaccine Pipeline

The WHO maintains a regularly updated pipeline tracker for a variety of pathogens, including Zika virus. It can be accessed at: http://www.who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet/en/

TABLE D.1 | SUMMARY OF THE ZIKV VACCINE PIPELINE, APRIL 2017

	Vaccine Platform	Research Groups
Phase 2 Trials	DNA vaccine	VRC and NIAID
Phase 1 Trials	ZPIV: Purified inactivated virus vaccine with aluminum hydroxide adjuvant	WRIR, NIAID, Beth Israel Deaconess Medical Center/Harvard, and Sanofi Pasteur
	DNA vaccine	Inovio Pharmaceuticals, GeneOne Life Science
	Measles vaccine virus vector	Themis Bioscience and Institut Pasteur
	Live attenuated chimeric vaccine	Instituto Butantan and NIH
	mRNA vaccine	Moderna Therapeutics and BARDA

Preclinical	Inactivated, aluminum adjuvant, whole virus vaccine	Takeda and BARDA
	Inactivated	Instituto Butantan, WHO, and BARDA
	Inactivated virus with aluminum adjuvant	Emergent BioSolutions
	Inactivated whole virus particle	NewLink Genetics
	Inactivated virus-like particles	PaxVax
	Inactivated	GlaxoSmithKline
	Inactivated	Bharat Biotech
	Self-amplifying mRNA	GlaxoSmithKline, VRC
	Live attenuated	Sanofi Pasteur
	Live attenuated	University of Texas Medical Branch and Instituto Evandro Chagas
	Chimpanzee adenovirus vectored	Jenner Institute
	Vesicular stomatitis virus vectored	Harvard University
	Subunit/peptide vaccine, recombinant variants of E protein	Protein Sciences
	Subunit/peptide vaccine, recombinant variants of insect cell line proteins	Hawaii Biotech
	Synthetic replilink peptide vaccine	Replikins
Subunit/peptide vaccine, recombinant vaccine from viral surface antigens	Bharat Biotech	

Sources: Information in table excerpted and adapted from Durbin, 2016, the WHO Vaccine Pipeline Tracker, and individual company press releases.

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