PREGNANT WOMEN & VACCINES AGAINST EMERGING EPIDEMIC THREATS

Ethics Guidance for Preparedness, Research, and Response

The PREVENT Working Group
EXECUTIVE SUMMARY

Recent epidemics, including Zika virus, Lassa Fever, Ebola, and H1N1 influenza, have highlighted the ways in which infectious disease outbreaks can severely—and at times uniquely—affect the health interests of pregnant women and their offspring.\(^1\) For some pathogens, pregnant women are at significantly higher risk of serious disease and death. Infection in pregnancy can also result in pregnancy loss or severe congenital harms. Even if the disease caused by the pathogen is no worse in pregnancy, the harms of infection in pregnant women can potentially affect two lives.

These serious and often disproportionate risks underscore the critical need to proactively consider the interests of pregnant women and their offspring in efforts to combat epidemic threats. This is especially true for vaccines, essential tools in the public health response to infectious diseases. Despite increasing support of maternal immunization strategies and efforts to develop certain vaccines specifically targeted to pregnant women, the vast majority of new vaccine products are rarely designed with pregnant women in mind. Moreover, widespread failure to appropriately include pregnant women in vaccine research means that evidence about safety and efficacy in pregnancy has been limited and late in coming. As a result, in numerous outbreaks and epidemics, pregnant women have been denied opportunities to receive vaccines that would have protected them and their offspring from the ravages of these diseases.

\(^1\) We use the term “women” throughout this document, and while we appreciate that individuals who do not 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 and having their health needs met that lie beyond the scope of this work. We use the term “offspring” throughout this report to broadly refer to fetuses as well as any persons born whose interests may be affected by in utero exposures to pathogens or vaccine administrations.

**This way of treating pregnant women in vaccine research and deployment is not acceptable. Business as usual can no longer continue.**

To ensure that the needs of pregnant women and their offspring are fairly addressed, new approaches to public health preparedness, vaccine research and development (R&D), and vaccine delivery are required. This Guidance provides a roadmap for the ethically responsible, socially just, and respectful inclusion of the interests of pregnant women in the development and deployment of vaccines against emerging pathogens. The Guidance is a product of the Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) Working Group—a multidisciplinary, international team of 17 experts specializing in bioethics, maternal immunization, maternal-fetal medicine, obstetrics, pediatrics, philosophy, public health, and vaccine research and policy—in consultation with a variety of external experts and stakeholders.

We recognize the recommendations contained in this Guidance will not always be easy to follow. For some, it will require a new way of thinking about pregnant women and vaccines. For many, it will require a commitment of will and of financial resources. Addressing inequities in biomedical research and public health rarely comes cheaply or without hard work. In terms of the lives saved and the suffering averted, the resources and the effort needed to ensure that pregnant women and their offspring are treated fairly will be more than worth it.
VISION
The guidance aims to realize a world in which:

Pregnant women are not unjustifiably excluded from participating in vaccine studies.

Pregnant women and their offspring benefit from advances in vaccine technologies and are not left behind as new vaccine products are developed.

Pregnant women have access to safe and effective vaccines to protect them and their offspring against emerging and re-emerging pathogenic threats.
RECOMMENDATIONS

PUBLIC HEALTH EMERGENCY PREPAREDNESS

RECOMMENDATION 1
Health information systems and infectious disease surveillance systems should be strengthened and integrated to ensure that data relevant to maternal, obstetric, and newborn health outcomes can inform scientific and public health responses to emerging pathogenic threats.

DIRECTED TO: public health authorities; the World Health Organization (WHO) and regional health organizations; developers and users of routine health information and global health security systems, including organizations with a focus on maternal and child health outcomes; organizations developing innovative approaches to data collection and surveillance; funders and sponsors of maternal health studies and global health surveillance

Routine health information systems and infectious disease surveillance systems are both essential to an appropriate and rapid response to emerging pathogenic threats. Collecting baseline data on maternal, obstetric, and newborn health can advance the interests of pregnant women and their offspring by enabling detection of increases in adverse events that may signal the presence of infectious disease threats. These baseline rates are also needed to help interpret whether adverse events surrounding pregnancy have any causal link to vaccination. Infectious disease surveillance systems should routinely include pregnancy status and maternal, obstetric, and newborn outcomes in case reports. These data, when integrated with baseline rates from health information systems, can help determine whether a circulating pathogen causes additional or more severe harms in pregnancy.

RECOMMENDATION 2
Evidence-based strategies to promote confidence about vaccination in pregnancy should be developed and implemented ahead of outbreaks, including stakeholder engagement with health care providers, women, their families, and their communities.

DIRECTED TO: public health authorities; health care providers; professional medical associations; medical and health training programs; community leaders; civil society organizations and vaccine advocacy groups; research institutes; funders and sponsors; the media

For immunization programs to be successful, it is critical that populations have confidence in the benefits of a vaccine and its safety, and in the health benefits of vaccination more broadly. Inadequate confidence in vaccines can be especially pronounced among pregnant women and those who care for them. Evidence about safety in pregnancy is limited because of the historic absence of vaccine trials in pregnant women. Moreover, pregnant women and health care providers are understandably concerned about fetal harm, and they are frequently bombarded with mixed messages about what may or may not be harmful in pregnancy. Working now to better understand and address the various sources and drivers of vaccine confidence among pregnant women and their communities will be critical to ensure appropriate vaccine uptake by pregnant women during outbreaks and epidemics.
RECOMMENDATION 3
Communication plans should be developed for clear, balanced, and contextualized dissemination of vaccine study findings, recommendations for vaccine use in pregnancy, and any pregnancy-specific adverse events.

DIRECTED TO: clinical investigators; scientific journal editors; funders and sponsors; public health authorities; global, regional, and local vaccine advisory groups; professional medical associations; regulatory authorities; civil society organizations and vaccine advocacy groups; the media

Because pregnant women, health providers, and the public often overestimate potential fetal harms associated with medications and biologics, effective communication in vaccine development and delivery is critical. In research studies, the required timely reporting of clinically relevant signals and findings on vaccine safety and efficacy in pregnancy to regulatory authorities is not enough. Effective communication to the public and to clinicians through a variety of channels, including traditional and social media, is essential. In an epidemic response that recommends vaccination in pregnancy, communication plans must be clear about any known risks to pregnant women and their offspring, and why the anticipated benefits of vaccination outweigh these risks. When immunization in pregnancy is not recommended, communication plans should be sensitive to fears and concerns about the pathogenic threat that pregnant women share with the rest of the population, and provide them with information about what alternatives, if any, are available to them. In both research and epidemic responses, one best practice for communicating reports of adverse pregnancy or birth outcomes is to present the findings alongside the best available information about the baseline rates of these adverse events, and to acknowledge that many of them have no known cause.

RECOMMENDATION 4
Research efforts that aim to advance vaccine development by using new technologies to study human immune system function and response should include investigations specific to pregnant women and their offspring.

DIRECTED TO: clinical investigators; basic research scientists; funders

Because pregnancy can alter immune response and because both maternal and fetal immune responses may change over the course of gestation, it is important that these foundational studies examine the distinctive characteristics of maternal and fetal immune systems. Understanding these differences could critically inform the development and identification of new vaccines that are safe and effective in pregnancy.

RECOMMENDATION 5
Mechanisms for incentivizing vaccine development for emerging and re-emerging infections and mitigating existing disincentives should include and address pregnancy-specific concerns of vaccine developers.

DIRECTED TO: policymakers; regulatory authorities; funders and sponsors; vaccine developers; civil society organizations and those who are positioned to influence vaccine research, adoption, and delivery, including WHO, the World Economic Forum, and the Coalition for Epidemic Preparedness Innovations (CEPI)

Vaccine developers and manufacturers face significant market challenges and uncertainties in pursuing products targeting emerging and re-emerging pathogens. These challenges can become even more complicated when vaccine products are studied in and ultimately offered to pregnant women—for whom there may be heightened concerns of legal and financial liability. Current mechanisms in place to encourage development of
beneficial biomedical products and protect developers and manufacturers against liability concerns—as well as new incentive programs being explored for vaccines against epidemic threats—need to be intentionally inclusive of the needs and interests of pregnant women.

**RECOMMENDATION 6**

To help ensure systematic and enduring change in the treatment of pregnant women in global vaccine policy and practices, the World Health Organization should convene a consultation of relevant stakeholders and experts. The Consultation should identify specific strategies to establish for pregnant women the presumption of inclusion in both vaccine research and deployment, including whether a dedicated, standing expert group is needed.

Throughout this Guidance we make multiple recommendations to help ensure that pregnant women and their offspring can fairly benefit from the protection that vaccines offer against emerging epidemic threats. These recommendations outline specific actions that need to be taken, but institutional change at every level—globally, regionally, and nationally—will be required to operationalize these new approaches and move advisory and decision-making bodies toward the new default of presumptive inclusion of pregnant women. To seed this institutional change and explore specific strategies for the

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**The Presumptive Inclusion of Pregnant Women**

“Presumption of inclusion” does not entail the automatic or absolute inclusion of pregnant women in every vaccine study or every vaccine campaign. Instead, a presumption of inclusion changes the default position. It normalizes the position that pregnant women are to be included in vaccine deployment programs and vaccine R&D. With inclusion of pregnant women as the default position, the burden of proof, both scientific and ethical, falls on those who want to argue for their exclusion. There will certainly be cases where the exclusion of pregnant women from a particular vaccine trial or vaccine campaign will be justified, but starting from a presumption of inclusion helps instantiate and maintain a fundamental shift in the way pregnancy and pregnant women are viewed in the field of vaccines.

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**Institutional change at every level will be required to establish a new default of presumptive inclusion of pregnant women.**

systematic consideration of pregnant women in international policies and practices governing vaccine research and delivery, WHO should convene a multi-day, global Consultation of relevant stakeholders. The Consultation should provide a critical opportunity to discuss and determine the best strategies to systematically integrate consideration of the interests of pregnant women and their offspring throughout all relevant WHO-supported activities, including whether a dedicated, standing group of relevant and diverse experts is needed. The Consultation should also consider ways to support regional and national public health authorities who may wish to establish similar expert groups.
VACCINE RESEARCH & DEVELOPMENT

RECOMMENDATION 7
Suitability for use in pregnancy should be a strong consideration in development and investment decisions for vaccines against emerging pathogenic threats.

DIRECTED TO: CEPI, U.S. Biomedical Advanced Research and Development Authority (BARDA), and other funders and sponsors; WHO emergency response teams, R&D Blueprint teams and TPP Working Groups; vaccine developers

If pregnant women, and the offspring they carry, are among those threatened by an emerging pathogen, then suitability for use during pregnancy should be an important vaccine development priority. Organizations investing in the vaccine pipeline against emerging pathogenic threats should try to ensure that, among candidates prioritized for development, at least some use platforms and adjuvants that would make them suitable for use in pregnancy. Early investment in options that are most likely to be acceptable in pregnancy can pave the way for pregnant women and their offspring to realize benefits from vaccine candidates that ultimately prove successful—and help ensure that they, like other population groups, will be protected against emerging infectious diseases. For pathogens that pose significantly greater threats in pregnancy—of fetal harm, maternal harm, or both—funding calls should designate greater investment priority to candidates likely to be suitable for use in pregnancy.

When pregnant women and their offspring are at higher risk of harm, it would be particularly unjust for their needs not to be included in vaccine development priorities.

RECOMMENDATION 8
When pathogens pose a risk of severe harm to pregnant women or their offspring and the most promising vaccine candidates are likely to be contraindicated for routine use in pregnancy, investments should be made in alternative vaccine candidates that could be more readily used in pregnancy.

DIRECTED TO: CEPI, BARDA, and other funders; vaccine developers

It is possible that the vaccine candidates that move most rapidly through the R&D pipeline are found to be problematic for use in pregnancy. Unless other vaccines with more favorable profiles for use in pregnancy are then prioritized, it is possible that pregnant women and their offspring will end up without any vaccine protection against the emerging pathogenic threat. This prospect is particularly dire when the target pathogen has more severe consequences in pregnancy. When pregnant women and their offspring suffer disproportionately compared with other population groups from an emerging infectious disease threat, justice calls for the vaccine enterprise to make every reasonable effort to bring to market a safe and effective product that pregnant women can use.

Pregnant women need to be on the agenda when decisions about investment and funding are made.
RECOMMENDATION 9
Non-clinical studies that are a prerequisite for clinical trials in pregnant women, such as developmental toxicology studies, should be initiated early in the clinical development of promising vaccine candidates, before efficacy trials are planned.

DIRECTED TO: CEPI, BARDA, and other funders and sponsors; vaccine developers; national regulatory authorities

Current regulatory guidance often requires that certain non-clinical studies must be completed prior to including pregnant women in clinical trials. Because pregnant women should be able to participate in large-scale efficacy studies conducted during outbreaks whenever the benefits outweigh the risks (see Recommendation 11), any non-clinical studies required prior to clinical evaluation in pregnant women should be conducted as soon as promising vaccine candidates move from phase 1 to phase 2 clinical trials.

RECOMMENDATION 10
Studies to assess immune responses to vaccines in pregnancy should be conducted before or between outbreaks whenever scientifically possible and ethically and legally acceptable.

DIRECTED TO: CEPI, BARDA, and other funders and sponsors; vaccine developers; clinical investigators

Although much of the work to evaluate vaccines in pregnancy will be done during outbreaks and epidemics (see Recommendation 11), there will be some cases in which it will be both beneficial and feasible to generate immunogenicity data in pregnancy before or between outbreaks. Because immune system functioning is altered in pregnancy, it is possible that a vaccine will be less immunogenic or induce atypical immune responses in pregnant women, with potential implications for its effectiveness as well as the dosing and frequency required in pregnancy to generate sufficient protection. Such immunogenicity studies would be particularly valuable if a correlate of protection for the vaccine has already been established. In the absence of an outbreak or epidemic, it may be difficult to demonstrate that studies to assess immune response in pregnant women have a favorable risk-benefit profile. However, there may be instances in which the future exposure to a pathogen among a particular population is likely enough to conclude that the potential benefits of being protected would outweigh the risks associated with a particular candidate vaccine.

RECOMMENDATION 11
Clinical development plans for investigational vaccines against emerging and re-emerging pathogens should include studies designed to evaluate vaccines in pregnancy. Pregnant women should have opportunities to enroll in vaccine studies conducted during outbreaks and epidemics whenever the prospect of benefit outweighs the risks to pregnant women, their offspring, or both.

DIRECTED TO: CEPI, BARDA, and other funders and sponsors; vaccine developers; clinical investigators and trial implementation partners; research ethics committees; national regulatory authorities

This recommendation rests on two claims of justice about the importance of treating pregnant women and their offspring fairly in the conduct of research on vaccines for emerging and re-emerging infections. The first of these justice claims pertains to pregnant women as a class: as a matter of equity, as well as public health, the evidence base for pregnant women should be as good as possible and generated as contemporaneously as possible to the evidence for the general population. The second, independent reason motivated by justice is that pregnant women, as the moral equals of others,
should have fair access to the prospect of direct benefit that may ensue from receiving an experimental vaccine. For both of these reasons, it is critical that vaccine research conducted during outbreaks include appropriate plans for research with pregnant women when there is a reasonable judgment that the prospective benefits of enrollment outweigh the risks.

**RECOMMENDATION 12**

Vaccine studies that include women of childbearing potential should have plans to systematically collect data on immunogenicity and pregnancy-specific indicators of safety from participants who are unknowingly pregnant at the time of exposure or become pregnant within a relevant window following vaccine administration.

- **DIRECTED TO:** CEPI, BARDA, and other funders and sponsors; vaccine developers; clinical investigators and trial implementation partners; research ethics committees; national regulatory authorities

In trials enrolling women of childbearing potential, including vaccine trials conducted in outbreak contexts, it is predictable that some women not known to be pregnant at the time of enrollment will nevertheless be pregnant at enrollment, or become pregnant in the course of the trial. Historically, data from inadvertent exposures during pregnancy have been a key source of information regarding the safety profiles of vaccines in pregnancy. Having a plan to systematically generate evidence from participants who are unknowingly pregnant at the time of administration also enables capturing data from vaccine exposures earlier in pregnancy than would be likely in trials prospectively enrolling pregnant women.

Wherever possible, systematic observational studies that are designed to capture inadvertent exposures to vaccine during pregnancy should also include longitudinal evaluation of safety, immunogenicity, and other relevant outcomes. Data from inadvertent exposures during pregnancy should be collected using standardized methods and case definitions and must be cautiously interpreted, particularly when adverse events occur in early pregnancy, as these very commonly occur unrelated to vaccine exposure.

**RECOMMENDATION 13**

Women participating in 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:** clinical investigators and trial implementation partners; vaccine developers; research ethics committees; national regulatory authorities

In vaccine trials that include prospectively enrolled pregnant women, participants who become pregnant after enrollment should be provided the opportunity to continue to receive vaccine doses after a renewed consent process. In trials that exclude pregnant women from prospective enrollment, determinations about continued dosing should be based on assessment of the potential benefits and harms specific to the circumstances of the pregnant participant, including possible risks associated with receiving an incomplete vaccination series and the risks already incurred from the first vaccination. In both cases, a robust re-consent process will be essential to allowing pregnant women to determine whether they want to receive additional doses. Regardless of whether they choose or are permitted to continue with the vaccine schedule, participants who become pregnant should be provided all study-related benefits and ancillary care to which they would otherwise be entitled.
RECOMMENDATION 14
When a pregnant woman of legal standing to consent is judged eligible to enroll or continue in a vaccine trial, her voluntary and informed consent should be sufficient to authorize her participation.

DIRECTED TO: clinical investigators and trial implementation partners; research ethics committees; national authorities in charge of governance and oversight of human subjects research

As a matter of respect, and as a key aspect of ensuring fair access to investigational vaccines, the consent of pregnant women who are judged eligible to participate in or continue receiving doses in a vaccine trial should be sufficient for participation. Pregnant women are the moral equals of other self-governing adults. Further, requiring the consent of additional actors can present a material barrier to the benefits research may offer to the offspring. At the same time, researchers should support pregnant women who wish to involve partners, family members, and other personal supports in decisions to join or remain in vaccine trials.

RECOMMENDATION 15
Experts in maternal and perinatal health, pediatrics, and research ethics should be involved in decisions about funding; trial design; research ethics oversight; and the generation, analysis, and evaluation of evidence on vaccine use in pregnancy.

DIRECTED TO: funders and sponsors; vaccine developers; clinical investigators; research ethics committees; national health authorities in charge of research governance and regulations; data safety monitoring boards

Pregnant women deserve that decisions affecting them will be made in careful, thoughtful, and evidence-based ways, involving the most informed experts possible. Experts in obstetrics and gynecology, maternal-fetal medicine, pediatrics, and neonatology, especially those who have experience with infectious diseases, immunology, and maternal immunization, have specialized knowledge that is critical to properly identifying and addressing the needs and interests of pregnant women and their offspring in research and development.

RECOMMENDATION 16
Whenever possible, the perspectives of pregnant women should be taken into account in designing and implementing vaccine studies in which pregnant women are enrolled or in which women enrolled may become pregnant.

DIRECTED TO: clinical investigators; vaccine developers; research ethics committees; community advisory boards; funders and sponsors; public health authorities

Community engagement and participatory-based approaches to biomedical research have been increasingly recognized as good practice in the design and conduct of human subjects research. In the context of vaccine studies enrolling pregnant women, soliciting the perspectives of pregnant women from the communities in which the research will be conducted offers a way to demonstrate respect, and can be critical to the success of a study. The perspectives of pregnant women can improve various aspects of study design by, for example, determining what information and outcomes are most important to pregnant women, ascertaining culturally relevant considerations for the consent process, and establishing the appropriate frequency and location of study visits based on the daily demands on women’s lives throughout pregnancy and after delivery.
VACCINE DELIVERY DURING THE EPIDEMIC RESPONSE

RECOMMENDATION 17
Pregnant women should be offered vaccines as part of an outbreak or epidemic response. Pregnant women should only be excluded if a review of available evidence by relevant experts concludes that the risks to pregnant women and their offspring from the vaccine are demonstrably greater than the risks of not being vaccinated.

DIRECTED TO: public health authorities; national immunization programs; recommending and advisory bodies, including professional medical associations, SAGE, and other relevant WHO advisory committees; teams overseeing the epidemic response, such as Public Health Emergency Operations Centers and incident management teams; organizations involved in vaccine delivery in the outbreak response, including UNICEF, MSF, and International Federation of Red Cross

Because pregnant women are the moral equals of others, and because there is nothing about being pregnant that would make them or their offspring less susceptible to the harms of emerging pathogenic threats, the default position of advisory bodies and public health authorities should be that pregnant women are offered vaccines alongside other affected populations during an epidemic response.

Any recommendations or decisions not to use vaccines in pregnancy during an outbreak or epidemic requires justification of exclusion based on a reasonable determination that the risks to pregnant women and their offspring from vaccination are demonstrably greater than the likely benefits of being protected from the pathogen. This determination should be made by relevant experts, including those in maternal, perinatal, and pediatric health.

The absence of evidence and the mere theoretical or even documented risk of fetal harm is generally not sufficient to justify denying pregnant women access to a vaccine in an outbreak or epidemic. Even when the risk of fetal harm from the vaccine is significant, if the likelihood and severity of harms from the pathogen are high enough for pregnant women and their offspring, then the benefits of vaccination may still outweigh the risks.

RECOMMENDATION 18
When there is a limited supply of vaccine against a pathogenic threat that disproportionately affects pregnant women, their offspring, or both, or when only one vaccine among several is appropriate for use in pregnancy, then pregnant women should be among the priority groups to be offered the vaccine.

DIRECTED TO: public health authorities; national immunization programs; teams overseeing the epidemic response, such as Public Health Emergency Operations Centers and incident management teams; WHO; organizations involved in vaccine delivery as part of the outbreak response, including UNICEF, MSF, and International Federation of Red Cross

It is not uncommon in outbreak and epidemic settings for vaccine demand to exceed supply. For some pathogenic threats, pregnant women and their offspring may be among the hardest hit groups; in these cases, as with any other high-risk group, they should be a priority in the allocation of a vaccine that is in short supply. Additionally, even when the threat is no worse for pregnant women than it is for other affected population groups, vaccinating a pregnant woman protects not only the pregnant woman but also her offspring. Particularly for high-consequence pathogens with significant mortality rates, there may be considerable additional benefit in vaccinating pregnant women.
During an epidemic, the default should be to offer vaccines to pregnant women alongside other affected populations.

RECOMMENDATION 19
When vaccines are offered to pregnant women during outbreaks or epidemics, prospective observational studies should be conducted with pregnant women and their offspring to further advance the evidence base for use in pregnancy.

- DIRECTED TO: vaccine manufacturers; public health and regulatory authorities; national immunization programs; organizations involved in vaccine delivery as part of the outbreak response, including UNICEF, MSF, and International Federation of Red Cross; researchers; funders; groups that oversee research with human subjects, including research ethics committees

Implementing prospective observational studies in pregnant women and their offspring who receive the vaccine as part of the outbreak or epidemic response provides an important opportunity to narrow the evidence gap between pregnant women and other population groups. If such studies are not conducted, decision-makers in future outbreaks and epidemics will be faced with the same evidence gap as current decision makers—an unacceptable outcome from both an equity and a public health perspective. Moreover, safety data obtained from evaluating a vaccine derived using a novel platform in pregnant women may inform future decision-making regarding the suitability of that platform for development of vaccines against other pathogens.

RECOMMENDATION 20
When vaccines are offered to pregnant women during outbreaks and epidemics, the consent of the pregnant woman should be sufficient to authorize administration whenever the pregnant woman is of legal standing to consent to medical care.

- DIRECTED TO: public health authorities; national immunization programs; teams overseeing the epidemic response, such as Public Health Emergency Operations Centers and incident management teams; organizations involved in vaccine delivery as part of the outbreak response, including UNICEF, MSF, and International Federation of Red Cross; clinicians and obstetricians; pregnant women and communities

As a matter of respect, and as a key aspect of ensuring fair access to vaccines during an outbreak or epidemic, when vaccines are offered to pregnant women, their consent should be sufficient to authorize administration. Women should be presumed to have authority for decisions about their own medical care. Women are no different from men in this respect, and pregnant women are no different than women who are not pregnant. All adults, regardless of gender or pregnancy status, have rights of self-determination over decisions that affect their bodies and their health. Pregnant women who wish to engage or consult with their partners or other family or friends in making their decisions about vaccination should be supported in doing so.

Ensuring that pregnant women have vaccines to protect them and their offspring will require generation of evidence from pregnant women.
RECOMMENDATION 21
When evidence supports a determination that the risk of serious maternal or fetal harm from the vaccine outweighs the vaccine’s benefits, pregnant women should be a priority group for access to alternative preventative or treatment measures.

DIRECTED TO: public health authorities; teams overseeing the epidemic response, such as Public Health Emergency Operations Centers and incident management teams; organizations involved in vaccine delivery as part of the outbreak response, including UNICEF, MSF, and International Federation of Red Cross; providers

Despite the best possible research and development efforts, the available vaccine for a given outbreak or epidemic may have sufficiently severe pregnancy-specific risks, even compared with the risks posed by the pathogen, that it is not made available to pregnant women. The moral objective remains, however, of giving pregnant women and their offspring as close to an equal chance of avoiding the harms of infection as the rest of the population. If they cannot be protected by immunization, then pregnant women, along with any other population group that cannot receive the vaccine, should be given preferential access to alternative preventive interventions and treatments.

RECOMMENDATION 22
When vaccines against emerging pathogens are not recommended for use in pregnancy, inadvertent vaccine exposures during pregnancy should be anticipated and mechanisms put in place for the collection and analysis of data from pregnant women and their offspring on relevant indicators and outcomes.

DIRECTED TO: public health and regulatory authorities; vaccine manufacturers; national immunization programs; funders and sponsors

Even when pregnant women are intentionally excluded from the vaccine response effort, it is reasonable to expect that some of the women who are vaccinated will be unknowingly pregnant at the time of vaccine administration, or will become pregnant within a relevant window of its administration. Collecting data about outcomes in these women and their offspring in the midst of an active outbreak or epidemic will be difficult and costly, but there are two sets of ethical and public health reasons why it is critically important to do so. First, collecting data from unintentional exposures to vaccine in pregnancy during an outbreak or epidemic affords an important opportunity to gather evidence about novel vaccine technologies and thus to help ensure that pregnant women are not left behind as vaccine technology advances. Second, research and public health communities have a responsibility to pursue evidence about the likelihood and nature of any associated risks pregnant women and their offspring face from these unintended exposures to inform personal and clinical decision-making.
no-fault compensation systems increase public confidence in vaccination. WHO, with support from partners at CEPI, World Economic Forum, and Harvard Global Health Institute, is currently exploring the establishment of a global no-fault compensation program that would specifically cover serious adverse events resulting from the use of non-licensed vaccines for emerging diseases with epidemic potential. We encourage those working on this compensation mechanism to explore ways this program can include features specific to vaccine administration in pregnancy—such as allowing for two claimants in the event that both the woman and her offspring suffer vaccine-associated adverse events.

Policymakers, regulatory authorities, sponsors, funders, civil society organizations, and those who are positioned to influence vaccine research and adoption should work together to identify global and country-specific incentive mechanisms for development and delivery of vaccines that pregnant women can use in the event of an outbreak, while exploring additional ways to mitigate disincentives that could keep beneficial vaccines from reaching pregnant women.

RECOMMENDATION 6
To help ensure systematic and enduring change in the treatment of pregnant women in global vaccine policy and practices, the World Health Organization should convene a consultation of relevant stakeholders and experts. The Consultation should identify specific strategies to establish for pregnant women the presumption of inclusion in both vaccine research and deployment, including whether a dedicated, standing expert group is needed.

Standard approaches to determining when pregnant women can be offered vaccines in the context of both research and delivery have too often operated on a presumption of exclusion—that pregnant women cannot or should not be eligible. This default mindset of exclusion, often without scientific or ethical justification, has done a great disservice to pregnant women and their offspring and

Box 6: The Presumptive Inclusion of Pregnant Women

“Presumption of inclusion” does not entail the automatic or absolute inclusion of pregnant women in every vaccine study or every vaccine campaign. Instead, a presumption of inclusion changes the default position. It normalizes the position that pregnant women are to be included in vaccine deployment programs and vaccine research and development. With inclusion of pregnant women as the default position, the burden of proof, both scientific and ethical, falls on those who want to argue for their exclusion. There will certainly be cases where the exclusion of pregnant women from a particular vaccine trial or vaccine campaign will be justified, but starting from a presumption of inclusion helps instantiate and maintain a fundamental shift in the way pregnancy and pregnant women are viewed in the field of vaccines. The presumption thus serves to reframe decisions about investments in vaccine research and development and about the design of vaccine delivery efforts in ways that are profoundly important from the standpoints of both public health and equity.

(See also Box 9).
must be changed. It has resulted not only in unjustifiably excluding pregnant women from specific vaccine trials or specific vaccine deployment efforts, but also in obscuring the interests of pregnant women from focal consideration in investments in vaccine research and public health programming, more broadly.

Throughout this Guidance we make multiple recommendations to help ensure that pregnant women and their offspring can fairly benefit from the protection that vaccines offer against emerging epidemic threats. These recommendations outline specific actions that need to be taken, but institutional change at every level—globally, regionally, and nationally—will be required to operationalize these new approaches and move advisory and decision-making bodies toward the new default of presumptive inclusion of pregnant women.

To seed this institutional change and explore specific strategies for the systematic consideration of pregnant women in international policies and practices governing vaccine research and delivery, WHO should convene a multi-day, global Consultation of relevant stakeholders.

Consultation participants should include representatives from regional regulatory networks and national regulatory authorities (NRAs), such as: the African Vaccine Regulatory Forum (AVAREF); the Pan American Pharmaceutical Regulation Harmonization Network (PANDRH); the Developing Country Vaccine Regulators’ Network (DCVRN); European Medicines Agency (EMA); U.S. Food and Drug Administration (FDA); and other NRAs, as well as from national ethics committees.

Experts in obstetrics and gynecology, maternal-fetal medicine, pediatrics, and neonatology, especially those with experience in infectious diseases, immunology, maternal immunization, and research and public health ethics should be present (see Recommendations 15 and 17), as well as stakeholder representatives from industry, implementation partners in research and emergency response, and funders.

The Consultation should provide a critical opportunity for representatives across relevant WHO programs, initiatives, clusters, teams, and advisory committees to discuss and determine the best strategies to systematically integrate consideration of the interests of pregnant women and their offspring throughout all WHO-supported activities relevant to vaccine R&D, maternal immunization, and emergency preparedness and response.

One such strategy that should be considered at the Consultation is the establishment of a Joint Pregnancy Expert Group on Immunization (JPEG). Structured as a standing body of interdisciplinary experts, the JPEG could provide guidance on use in pregnancy for both routine vaccination and vaccination in public health emergencies. This interdisciplinary expert group could jointly report to existing WHO advisory groups, such as the Strategic Advisory Group of Experts (SAGE) on

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vi. This is consistent with various CIOMS International Ethical Guidelines on equitable distribution of benefits and harms of research, which state that: inclusion and exclusion criteria should not be based on potentially discriminatory criteria unless there is a sound ethical or scientific reason; for research in disease outbreaks, adequate justification is given whenever particular populations are excluded; and when under-representation of groups results in or perpetuates health disparities, equity may require special efforts to include members of those groups in research.

vii. Although the focus of this recommendation is on specific vaccine products and maternal immunization, particularly in outbreak contexts, the Consultation may be a useful platform to explore broader strategies to address the interests and unmet needs of pregnant women and their offspring as they pertain to the development and delivery of a wider range of biomedical interventions.
We believe there are compelling reasons for establishing JPEG. Creating a standing body at the World Health Organization devoted to pregnant women and vaccines will bring global focal attention to maternal immunization. The JPEG will send an unmistakable signal to the global health community that pregnant women and their offspring, no less than other members of the population, should be permitted to benefit from the advances in health that vaccines offer, and that there are responsible ways to ensure that they do.

Moreover, making determinations about what is in the best interests of pregnant women and their offspring during an emerging outbreak or epidemic often entails multiple and complex assessments and the synthesis of rapidly emerging data from many settings. It is unrealistic and inefficient to expect every locality to have the resources to be able to convene the expertise necessary to assess vaccine use in pregnancy during an outbreak or epidemic. However, absent an appropriate and timely process for making these assessments, pregnant women and their offspring will continue to be seriously disadvantaged—with the default being their exclusion from programs that deliver beneficial vaccines in emergency responses.

The Consultation should also include consideration of ways to support regional and national public health authorities who may wish to establish similar groups of relevant and diverse experts to advise their National Immunization Technical Advisory Groups (NITAGs), Regional Immunization Technical Advisory Groups (RITAGs), and emergency response teams. In addition, the Consultation should address approaches to facilitate communication and collaboration between national, regional, and global advisory groups on pregnancy during outbreaks.

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viii. The JPEG could be modelled after the similarly structured Joint Technical Expert Group (JTEG) on malaria vaccines, which was convened by the Immunization, Vaccines, and Biologicals Department (IVBD) and the Global Malaria Program (GMP) to provide advice on malaria vaccine development to both SAGE and the Malaria Policy Advisory Committee (MPAC). For more on the JTEG, see Kaslow DC, Biernaux S. RTS, S: Toward a first landmark on the Malaria Vaccine Technology Roadmap. Vaccine. 2015 Dec 22;33(52):7425–32 and WHO Initiative for vaccine research/global malaria programme joint technical expert group (JTEG) on malaria vaccines entering pivotal phase 3 trials & beyond (April 2009–February 2016). Terms of References. Accessed 8 Aug 2018. Available from: www.who.int/immunization/research/committees/jteg/en.
engagement platforms already being planned for the research, such as a community advisory board. Another option is to conduct dedicated formative research with pregnant women or to establish an advisory board for the trial that is composed of pregnant women and their family members.

Because a number of standard protocols for vaccine efficacy trials are being developed in advance of epidemics to enable rapid implementation, there should be ample opportunity to engage pregnant women as well as other stakeholders in the development of these protocols. 25,138,139

III. VACCINE DELIVERY DURING THE EPIDEMIC RESPONSE

RECOMMENDATION 17
Pregnant women should be offered vaccines as part of an outbreak or epidemic response. Pregnant women should only be excluded if a review of available evidence by relevant experts concludes that the risks to pregnant women and their offspring from the vaccine are demonstrably greater than the risks of not being vaccinated.

- DIRECTED TO: public health authorities; national immunization programs; recommending and advisory bodies, including including professional medical associations, SAGE, and other relevant WHO advisory committees; teams overseeing the epidemic response, such as Public Health Emergency Operations Centers and incident management teams; organizations involved in vaccine delivery in the outbreak response, including UNICEF, MSF, and International Federation of Red Cross

Because pregnant women are the moral equals of others, and because there is nothing about being pregnant that would make them or their offspring less susceptible to the harms of emerging pathogenic threats, the default position of advisory bodies and public health decision-makers should be that pregnant women are offered vaccines alongside other affected populations during an epidemic response. Any recommendations or decisions not to use vaccines in pregnancy during an outbreak or epidemic requires justification of exclusion based on a reasonable determination that the risks to pregnant women and their offspring from vaccination are demonstrably greater than the likely benefits of being protected from the pathogen.

An assessment of the comparative risks and benefits of vaccination in pregnancy during an outbreak should take into account the same 6 considerations identified for the appropriateness of including pregnant women in research: 1) the likelihood of infection; 2) the likelihood and severity of harms to pregnant women and their offspring from infection; 3) the likelihood that the vaccine will protect against the potential risks of infection in both pregnant women and their offspring; 4) the likelihood and severity of risks to pregnant women and their offspring from receiving the vaccine; 5) the availability of safe and effective alternative prevention options; and 6) the availability of safe and effective treatment options. However, at the time of implementing a vaccine campaign, compared with the trial context, there is typically more evidence available to inform these assessments. Table A provides more detail about these considerations, with side-by-side comparisons of the two different contexts.

Risk-benefit assessments should be informed by expert review of the best available evidence. The establishment of an WHO standing body of interdisciplinary experts dedicated to advising on vaccine use in pregnancy, as proposed for consideration in Recommendation 6, can help fulfill this requirement. So, too, would
be the establishment of any regional or local counterparts.

The considerations in Table A are likely to play out differently for different combinations of pathogenic threats and vaccine countermeasures. Advisory committees, decision-makers, and the experts they engage will need to weigh the evidence available at the time as best they can to reach informed and fair judgments.

In some cases, there may be substantial data from intentional administrations or inadvertent exposures during pregnancy in the context of clinical trials or in earlier outbreaks to establish the safety of the vaccine in pregnant women. Alternatively, the vaccine may be new but developed using a platform and/or adjuvant that has been widely and safely used in other maternal immunizations.

In other cases, it may be advantageous to offer pregnant women vaccines with non-ideal characteristics for pregnancy because the protective benefits of the vaccine outweigh risks. The absence of evidence and the mere theoretical or even documented risk of fetal harm is generally not sufficient to justify denying pregnant women access to a vaccine in an outbreak or epidemic. Even when the risk of fetal harm from the vaccine is significant, if the likelihood and severity of harms from the pathogen are high enough for pregnant women and their offspring, then the benefits of vaccination may still outweigh the risks. (See Box 12) For example, while the live-attenuated yellow fever vaccine is not routinely offered to pregnant women, it is widely endorsed for use during epidemics to protect pregnant women and their offspring against the far greater risks of yellow fever infection.

**Box 12: Theoretical Risks of Live Vaccines in Pregnancy versus Documented Associated Harms**

Routine administration of live vaccines to pregnant women has been generally contraindicated because of concerns about fetal harm. However, not all live vaccines pose equal concern. Concern is greatest for those live vaccines that replicate systemically and could potentially cross the placenta. Despite unintended exposures during pregnancy to several of these types of live vaccines (e.g., rubella, yellow fever, and smallpox vaccines) in hundreds to thousands of women, convincing evidence of fetal harm has only been demonstrated for smallpox vaccine (a small increased risk of birth defects [2.4% vs. 1.5%] among women vaccinated in the first trimester; a total of 21 cases of fetal vaccinia reported in the literature). For this reason, offering yellow fever and smallpox vaccines to pregnant women at high risk of infection has been advised, based upon the assessment that potential benefits far outweigh risks. When novel live vaccines are being developed for emerging pathogens, it will be impossible to prospectively assess the risk of fetal harm through transplacental transmission of live-attenuated vaccine candidates that replicate systemically. To ensure that pregnant women have access to vaccines with reassuring safety data, investments should be made in vaccine candidates that are most likely to be acceptable in pregnancy (Recommendations 7 and 8). In addition, since situations will likely arise in which women are unintentionally exposed to these types of live vaccines during pregnancy, it will be critical to systematically collect data on pregnancy-specific indicators of safety to inform a risk-benefit assessment (Recommendations 12 and 22).
Consider also the rVSV-ZEBOV Ebola vaccine. This vaccine would likely not be viewed as appropriate for use in pregnancy outside the context of an Ebola outbreak. Currently, however, it is the only Ebola vaccine that has successfully completed efficacy trials.\textsuperscript{146} Given the harms associated with Ebola infection in pregnancy, including maternal mortality ranging from 70–90\% and near 100\% fetal demise, the potential benefits of offering the vaccine clearly outweigh the potential harms in the context of a high incidence outbreak setting.\textsuperscript{2,3}

**RECOMMENDATION 18**
When there is a limited supply of vaccine against a pathogenic threat that disproportionally affects pregnant women, their offspring, or both, or when only one vaccine among several is appropriate for use in pregnancy, then pregnant women should be among the priority groups to be offered the vaccine.

- **DIRECTED TO:** public health authorities; national immunization programs; teams overseeing the epidemic response, such as Public Health Emergency Operations Centers and incident management teams; WHO; organizations involved in vaccine delivery as part of the outbreak response, including UNICEF, MSF, and International Federation of Red Cross

It is not uncommon in outbreak and epidemic settings for vaccine demand to exceed supply. Numerous groups have proposed criteria for determining how to ethically set priorities among different groups of potential vaccine recipients.\textsuperscript{147,148,149,150} Most acknowledge that groups who face greater risks of harm from the infection have a greater claim on vaccines than those who face lesser risks. For some pathogenic threats, such as Lassa fever, pregnant women and their offspring may be among the hardest hit groups and should, like any other high-risk group, be a priority in the allocation of a vaccine that is in short supply.

An additional argument in favor of placing a priority on pregnant women in vaccine scarcity settings is that vaccinating a pregnant woman protects not only the pregnant woman but also her offspring. Particularly for high-consequence pathogens with significant mortality rates, there may be additional benefit when pregnant women are vaccinated. It is not only their lives, but the lives of the children they bear that stand to be saved. This argument applies even when the threat is no worse for pregnant women than it is for other affected population groups.

Yet another context in which pregnant women may justifiably be made a priority is when more than one vaccine is available to combat an outbreak or epidemic, but one vaccine is distinctly preferable for use in pregnancy. Here, it may be appropriate to allocate the preferable vaccine first for administration to pregnant women, as well as to any other group who might benefit from that vaccine’s specific characteristics.

As is the case with all allocation criteria for scarce resources in a public health emergency, the reasons why some groups are prioritized should be communicated clearly to the public. Transparency is crucial to sustaining public trust during epidemics.\textsuperscript{8,10,23}
### Table A: Considerations for Assessing Risks & Benefits of Including Pregnant Women in Vaccine Research & Delivery

<table>
<thead>
<tr>
<th>Considerations</th>
<th>Research Context</th>
<th>Specific Dimensions of the Consideration &amp; Expanded Definition</th>
<th>Deployment Context</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Likelihood of infection</td>
<td>» Likelihood of exposure</td>
<td>» Likelihood of exposure</td>
<td>» Likelihood of exposure</td>
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<td></td>
<td>» Susceptibility to infection</td>
<td>» Susceptibility to infection</td>
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<td>» Susceptibility of the pregnant woman</td>
<td>» Susceptibility of the pregnant woman</td>
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<td></td>
<td>» Potential for vertical transmission of pathogen to the offspring</td>
<td>» Potential for vertical transmission of pathogen to the offspring</td>
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<tr>
<td>2. Probability and severity of harms of infection to pregnant women and offspring</td>
<td>» Types of maternal, obstetric, and child harms</td>
<td>» Types of maternal, obstetric, and child harms</td>
<td>» Types of maternal, obstetric, and child harms</td>
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<td></td>
<td>» Morbidity</td>
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<td>» Pregnancy loss</td>
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<td>» Pre-term labor</td>
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<td>» Short- and long-term congenital harms</td>
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<td>» Probability and severity of these harms often vary based on gestational timing of infection and may vary between pregnant woman and offspring (see below)</td>
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<td>Maternal and Obstetric:</td>
<td>Some pathogens cause high rates of mortality and severe morbidity, with short-term and potential long-term effects on a woman’s health. In some cases, the severity of effects is significantly heightened in pregnancy, with variable virulence across different stages of gestation. Additionally, infection may result in pregnancy loss, which can have adverse health and psychological consequences for women.</td>
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<td>Offspring:</td>
<td>For certain pathogens, the primary concern is the congenital harm from fetal infection during pregnancy. However, a broader range of pathogens can have detrimental congenital effects – with short- or long-term ramifications – as a result of maternal infection. Even if the pathogen never crosses the placenta, harm to the fetus can arise from maternal health consequences of infection, particularly if the pathogen causes symptoms such as a high fever, anemia, or obstetric complications such as premature labor and delivery or maternal death.</td>
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<tr>
<td>3. Prospect of immune protection from vaccine</td>
<td>» Based on data from clinical trials (phases 1 and 2)</td>
<td>» Based on data from clinical trials (phases 2, 3, 4)</td>
<td>» Based on data from clinical trials (phases 2, 3, 4)</td>
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<td></td>
<td>» Magnitude and frequency of immune responses</td>
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<td>» Correlate of protection (if known)</td>
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<td>» Special considerations relevant to pregnant women and their offspring (e.g., placental transfer of antibody; sterilizing immunity against pathogens that can infect fetus)</td>
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<td><strong>Data related to the magnitude and frequency of relevant immune responses may suggest that a vaccine candidate will protect against disease caused by the pathogen. Depending on the studies completed prior to large-scale efficacy trials, there may be more or less evidence that a vaccine will induce an adequate immune response. This can be especially true for vaccines being developed against emerging threats, given accelerated pathways for clinical testing that may differ from standard approaches. Data from prior studies, including pre-clinical and clinical trials that assess immunogenicity and other indicators of efficacy (e.g., challenge trials in non-human primates), will provide varying degrees of evidence about anticipated protective effects of a vaccine.</strong></td>
<td><strong>Indicators from prior studies, including pre- and post-licensure studies on immunogenicity, efficacy, and effectiveness, can provide information on the protective effects of a vaccine. There are efficacy indicators that may be particularly important during pregnancy — for example, sterilizing immunity may be required to fully protect against congenital Zika syndrome. Additionally, if immunogenicity studies have been done in pregnancy, this can further inform the anticipated protection a vaccine will confer and whether there are any clinically meaningful differences in how the vaccine performs in pregnant women.</strong></td>
</tr>
</tbody>
</table>

| 4. Likelihood and severity of vaccine-associated harms to the pregnant woman or offspring | » Safety and reactogenicity  
  o Based on data from prior studies of the specific vaccine candidate  
  o Based on evidence from vaccines using similar platforms | » Safety and reactogenicity  
  o Based on data from prior studies of the specific vaccine candidate, including observational studies from previous deployments of the vaccine in response to past outbreaks  
  o Based on evidence from vaccines using similar platforms | » Probability and severity of these harms may vary based on gestational timing of vaccine administration and may vary between pregnant woman and offspring (see below)  
  Maternal and Obstetric: Adverse events (AEs) following vaccine administration range from common mild events (e.g., transient arthralgia) to very rare severe events (e.g., Guillain-Barré syndrome, anaphylaxis). Data on the likelihood and severity of vaccine-associated AEs should be considered against the probability and magnitude of benefit from protection against the pathogenic threat. Available evidence informing whether the vaccine and/or the pathogen may increase the risk of pregnancy loss should also be considered.  
  Offspring: Some vaccine candidates employ platforms and adjuvants with a long history of fetal safety. Others, like replication-competent vaccines, may raise particular concerns in pregnancy based on theoretical risks of the vaccine virus causing harm to the fetus. Although convincing evidence of fetal harm has only been demonstrated for smallpox vaccine (see Box 12), biological plausibility and potential fetal harms should be considered among other factors in the risk-benefit assessment for any vaccine platform. For many vaccine components and platforms, particularly novel ones like nucleic acid-based vaccines, there is limited evidence available on potential associated fetal harms. As the evidence base grows, the best available data should be used to assess the known likelihood and severity of congenital harms across candidate platforms. | » Probability and severity of these harms may vary based on gestational timing of vaccine administration and may vary between pregnant woman and offspring (see below) |
### Table A: Considerations for Assessing Risks & Benefits of Including Pregnant Women in Vaccine Research & Delivery

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</table>
| **5. Availability of safe and effective alternative prevention options** | » Relevant considerations for alternative preventives  
○ Safety (generally and in pregnancy)  
○ Efficacy (generally and in pregnancy)  
○ Durability, sustainability, and adherence factors  
○ Availability and accessibility in the area(s) where research is being conducted | » Relevant considerations for alternative preventives  
○ Safety (generally and in pregnancy)  
○ Efficacy (generally and in pregnancy)  
○ Durability, sustainability, and adherence factors  
○ Availability and accessibility in the area(s) affected by the epidemic |

The availability and effectiveness of alternative forms of prevention will vary based on the type of epidemic threat and the context in which the outbreak is occurring. In some cases, there may be available and acceptable alternatives that pregnant women can use for prevention in an outbreak that may be preferable, depending how they compare to the vaccine. In other cases, the alternative prevention options may be inadequate or their availability may be limited, and receiving the vaccine may be preferable to relying on alternative strategies. In some instances, the best alternative preventative interventions for the general population may have well-established risks in pregnancy and should be avoided in favor of safer options.

| **6. Availability of safe and effective treatment options** | » Relevant considerations for treatments  
○ Safety (generally and in pregnancy)  
○ Efficacy (generally and in pregnancy)  
○ Availability and accessibility in area(s) where research is being conducted | » Relevant considerations for treatments  
○ Safety (generally and in pregnancy)  
○ Efficacy (generally and in pregnancy) |

The existence, availability, effectiveness, and safety profiles in pregnancy of therapeutic options may influence assessments of whether study participation offers the prospect of net benefit. For certain emerging pathogens, there may not yet be any effective treatment. When treatments exist, they may not have evidence of safety, dosing, and efficacy for use in pregnancy — and in some cases, treatment options may be known teratogens. Even when safe and effective options exist, their availability within a given epidemic context may limited.

The existence, availability, effectiveness, and safety profiles in pregnancy of therapeutic options may influence assessments of whether pregnant women and their offspring are better off receiving or foregoing vaccination during an epidemic or outbreak. For certain emerging pathogens, there may not yet be any effective ways to treat the infection. When treatment options exist, they may not have evidence of safety, dosing, and efficacy in pregnancy – and in some cases, treatment options may be known teratogens. Even when safe and effective options do exist, their availability within a given epidemic context may be limited.

RECOMMENDATION 22
When vaccines against emerging pathogens are not recommended for use in pregnancy, inadvertent vaccine exposures during pregnancy should be anticipated and mechanisms put in place for the collection and analysis of data from pregnant women and their offspring on relevant indicators and outcomes.

- DIRECTED TO: public health and regulatory authorities; vaccine manufacturers; national immunization programs; funders and sponsors

For most immunization efforts in response to outbreaks, women of childbearing potential will comprise a significant subset of the target population. Even when pregnant women are intentionally excluded from the vaccine response effort, it should be expected that some of the women who are vaccinated will be unknowingly pregnant at the time of vaccine administration or will become pregnant within a relevant window of its administration. Collecting data about outcomes in these women and their offspring in the midst of an active outbreak or epidemic will be difficult and costly. However, there are two sets of ethical and public health reasons why it is critically important to do so.

First, collecting data from unintentional exposures to vaccine in pregnancy during an outbreak or epidemic affords an important opportunity to gather evidence about novel vaccine technologies and thus to help ensure that pregnant women are not left behind as vaccine technology advances. Gathering data from women who are unknowingly pregnant when they receive vaccine and subsequently from their offspring could be critical and uniquely informative to building an evidence base on safety and efficacy in pregnancy of novel vaccine technologies, given that these data may be difficult to otherwise obtain. For example, studies of oral cholera vaccine given to women unintentionally during pregnancy in Bangladesh, Guinea, Malawi, and Zanzibar were instrumental in establishing the safety profile of the vaccine in pregnancy and shifting the WHO recommendation in support of including pregnant women in oral cholera vaccine campaigns. ¹⁶⁰

The second set of reasons has to do with the importance of having evidence for both personal and clinical decision-making about the likelihood and nature of any risks to pregnant women or their offspring associated with vaccine administration in early pregnancy. Research and public health communities have a responsibility to pursue evidence that will allow for the best possible counseling on the implications of unintentional exposures during pregnancy. The price of ignorance in the face of unintended exposures is significant. We know from the experience with live-attenuated rubella vaccines that hundreds of women inadvertently exposed during pregnancy chose to terminate their pregnancies, presumably due to concerns about unknown fetal harm. ⁷⁴,¹⁶¹,¹⁶²,¹⁶³ Yet worries about vaccine-associated congenital rubella syndrome turned out to be unfounded, with not a single case documented from thousands of unintentional exposures worldwide.¹²³ Furthermore, pregnant women who are vaccinated prior to finding out they are pregnant 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 and whether they should receive another dose of vaccine after delivery to ensure protection in future epidemics.
Box 14: Active and Passive Vaccine Surveillance Systems to Advance the Evidence Base on Vaccines in Pregnancy

Existing vaccine surveillance programs for monitoring adverse events following immunization (AEFI) can be useful tools to study both intentional and unintentional vaccine administrations in pregnancy (Recommendations 19 and 22). Various countries and regions have mandatory requirements for passive reporting of any adverse events potentially associated with immunization, including the U.S. Vaccine Adverse Event Reporting System (VAERS), the EU EudraVigilance, and the Chinese National AEFI Information System (CNAEFIS). Although the ability to draw conclusions from passive surveillance systems is limited due to potential reporting bias and unknown denominators, these systems can serve as important mechanisms to identify safety signals for vaccination in pregnancy that require further study. They are especially useful and cost-effective for monitoring vaccines over the longer term, enabling the detection of rare adverse events that may occur in a very small percent of the vaccinated population. These passive surveillance systems can be leveraged to enhance the evidence base on vaccine use in pregnancy by adding more targeted questions about pregnancy status, gestational timing of immunization, and pregnancy-specific outcomes to the data collection forms.

For newer vaccines, active surveillance mechanisms can be critical tools to build upon pre-licensure safety data once the vaccine is introduced to the broader population, without some of the methodological shortcomings inherent in passive systems. In the U.S., various active vaccine surveillance programs, such as the Post-Licensure Rapid Immunization Safety Monitoring (PRISM), Vaccines and Medications in Pregnancy Surveillance System, and Vaccine Safety Datalink, are being used to build the safety profile of 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-market studies—including those focused on safety in pregnancy. In recent years, there has been increasing focus on the systematic surveillance for AEFI for pregnant women and their offspring. 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.
### MEMBERS OF THE PREVENT WORKING GROUP

<table>
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<tr>
<th>Name</th>
<th>Role</th>
<th>Institution/Organization</th>
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<tbody>
<tr>
<td>Ruth Faden</td>
<td>Principal Investigator</td>
<td>Johns Hopkins Berman Institute of Bioethics</td>
</tr>
<tr>
<td>Margaret Little</td>
<td>Co-Investigator</td>
<td>Georgetown University Kennedy Institute of Ethics</td>
</tr>
<tr>
<td>Jon Abramson</td>
<td></td>
<td>Wake Forest University School of Medicine</td>
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<tr>
<td>Alejandro Cravioto</td>
<td></td>
<td>Universidad Nacional Autónoma de México Faculty of Medicine</td>
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<tr>
<td>Bruce Gellin</td>
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<td>Sabin Vaccine Institute</td>
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<tr>
<td>David C. Kaslow</td>
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<td>PATH Essential Medicines</td>
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<td>Florencia Luna</td>
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<td>FLACSO-Argentina Bioethics Program &amp; CONICET</td>
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<td>Jeanne Sheffield</td>
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<td>Johns Hopkins University School of Medicine</td>
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<td>Swati Gupta</td>
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<td>International AIDS Vaccine Initiative (IAVI)</td>
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<td>Sonali Kochhar</td>
<td></td>
<td>Global Healthcare Consulting</td>
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<tr>
<td>Carla Saenz</td>
<td></td>
<td>Pan American Health Organization Regional Program on Bioethics</td>
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<td>Richard Beigi</td>
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<td>Magee-Womens Hospital of University of Pittsburgh Medical Center</td>
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