Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies
PREVENT

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PREGNANT WOMEN & VACCINES AGAINST EMERGING EPIDEMIC THREATS

Ethics Guidance for Preparedness, Research, and Response

The PREVENT Working Group

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Developed by the
Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) Working Group

Johns Hopkins Berman Institute of Bioethics
The Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) Project

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PREFACE

Biomedical advancements have brought us tremendous innovations in the past century, yet there has long been a gender problem—in the ways we understand disease presentation, in the ways we pursue development of new drugs and biologics, and ultimately in the ways science and medicine address the health needs of women. In the 1990s, prominent reports brought to light the extent to which the interests of women were underrepresented in biomedical research efforts and the harms associated with their inadequate inclusion in the research agenda. One of us (RF) was the co-chair of the Institute of Medicine committee that authored an influential report of that period, *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*.

Much progress has been made in the last two decades to better address the health needs of women. However, one recommendation of that IOM report, specific to *pregnant women*, gained little traction. More than twenty years later, tremendous evidence gaps about the appropriate dosing and use of drugs and biologics in *pregnancy* persist. Despite the fact that most women need some form of medication during their pregnancy—for chronic and acute conditions—the vast majority of drugs that have come to market have little to no data on their safe and effective use in pregnancy. This state of affairs is unacceptable. A new paradigm must be forged to safely and responsibly include pregnant women in research so that all pregnant women and their developing children will ultimately benefit from interventions critical to their health and wellbeing.

In the mid-2000's, three of us (AL, ML, and RF) began a collaborative research program to change the status quo and forge this new paradigm. In 2009, we launched the *Second Wave Initiative*, a collaborative academic effort to advocate for, and help find, ethically and scientifically responsible solutions for increasing our knowledge base for the treatment of pregnant women who face medical illness. In the intervening years, the Second Wave Initiative has helped galvanize scholarship and advocacy in the United States, and around the world.

This Guidance has benefited from the Second Wave and other intersecting collaborations across the years. Several of us, as part of a larger team, are working on another grant funded by the U.S. National Institutes of Health, the PHASES project—*Pregnancy & HIV/AIDS: Seeking Equitable Study* (PI: AL), which is developing an ethical framework for research at the juncture of pregnancy, HIV, and its co-morbidities. In addition, RF and RK have collaborated for many years on the ethics of vaccine policy and epidemic response.

Work on the present Guidance began in 2016, when the Zika virus was shining a global spotlight on the devastation that infectious disease epidemics can cause in pregnancy. We received a grant from the Wellcome Trust to provide ethics guidance at the intersection of pregnancy, vaccines, and emerging and re-emerging epidemic threats. The PREVENT project—*Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies* (PI: RF)—addresses research with pregnant women in the distinctive context of biologics. In our first year, we focused on the special

case of pregnancy and Zika virus vaccines. The report of the Ethics Working Group on ZIKV Research and Pregnancy, *Pregnant Women and the Zika Virus Vaccine Research Agenda: Ethics Guidance on Priorities, Inclusion, and Evidence Generation*, was released in June, 2017.

We are delighted now to be releasing our second Guidance, *Pregnant Women & Vaccines Against Emerging Epidemic Threats: Ethics Guidance for Preparedness, Research, and Response*, authored by the PREVENT Working Group.

This Guidance benefits enormously from the Zika Report and from the on-going work on PHASES. Further, much of the foundational thinking about pregnant women, fairness and equity, and research ethics in both PREVENT and PHASES draws on the common foundation of the Second Wave Initiative.

Across all this work is the shared theme that pregnant women cannot be ignored as the scientific and biomedical communities continue to innovate and develop new medicines and tools to improve health. This Guidance forms a key piece in an important and growing body of work, by us and by others, to ensure that pregnant women benefit fairly from advances in biomedicine.

Ruth Faden, Ruth Karron, Carleigh Krubiner,
Maggie Little, Anne Lyerly

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This Guidance benefitted from the comments and input from a wide range of experts who participated in individual or group consultations with members of the Working Group. These discussions provided us with invaluable insights that critically shaped the content the guidance and helped ensure that our recommendations accounted for the most-up-date evidence and practical realities of vaccine development and deployment. We are thankful to all of the individuals who shared their time and expertise to advance this guidance, among them: Jenn Braverman, Paula Bryant, Linda O. Eckert, MD, Peggy Hamburg, Wayne Koff, Nicole Lurie, Bonnie Maldonado, Sophie Matthewson, Flor Muñoz-Rivas, Åge Nærdal, Lisa Noguchi, Dawn O'Connell, Saad Omer, Walter Orenstein, Michael Pfleiderer, Gregory A. Poland, MD, MACP, FIDSA, FRCP, Helen Rees, Annette Rid, Melanie Saville, Ajoke Sobanjo-ter Meulen, and Adam Soble. Additional thanks to Wing-yun Cheung for her support in bringing together the roundtable discussion at the World Vaccine Congress.

We are also thankful to our colleagues who shared their thoughts and feedback at the various venues and meetings where sections of the draft Guidance were shared, including attendees at the Ethox Centre Workshop on the Ethical Design of Vaccine Trials in Emerging Infections, the IDSOG 2017 Annual Meeting, the ASBH 2017 Annual Conference, the 2nd meeting of the U.S. HHS Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC), the ASTMH 2017 Annual Meeting, the PDVAC Consultation on Nucleic Acid Vaccines, the 2018 World Vaccine Congress, the 2018 Annual Conference on Vaccinology Research and the Johns Hopkins Berman Institute of Bioethics/University of Maryland Carey Law School 2018 Spring Research Retreat.

This Guidance is built upon a first set of recommendations developed under this grant, specifically in the context of the Zika virus: "Pregnant Women & the Zika Virus Vaccine Research Agenda: Ethics Guidance on Priorities, Inclusion, and Evidence Generation." We extend our deepest thanks to the co-authors of our Zika report who served on the Ethics Working Group on ZIKV Research & Pregnancy (Allison August, Nancy Kass, Ricardo Palacios, Alexander Precioso, Beatriz da Costa Thomé), as well as the 60+ individuals we consulted with during the development of the Zika guidance.

We are incredibly appreciative of our project team members and staff, who provided tremendous research and administrative support from the earliest stages of the project to the final draft of the guidance. Special thanks to Elana Jaffe and Marisha Wickremsinhe who dedicated countless hours reviewing the literature, organizing consultation calls and meetings, supporting Working Group meetings, and working with the team through multiple iterations of the guidance, among many other inputs that are too numerous to name. Additional thanks to Rachel Fabi, Kelly Whalen, Amelia Hood, and the communications and administrative teams at Johns Hopkins University, the University of North Carolina, and Georgetown University who supported this work.

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ACRONYMS

ACOG	American College of Obstetrics and Gynecology
AE	Adverse Events
AEFI	Adverse Events Following Immunization
AVAREF	African Vaccine Regulatory Forum
BARDA	U.S. Biomedical Advanced Research and Development Authority
CDC	U.S. Centers for Disease Control and Prevention
CEPI	Coalition for Epidemic Preparedness Innovations
CIOMS	Council for International Organizations of Medical Sciences
CNAEFIS	Chinese National AEFI Information System
DCVRN	Developing Country Vaccine Regulators' Network
DSMB	Data Safety Monitoring Boards
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
GAIA	Global Alignment of Immunization safety Assessment in Pregnancy
Gavi	Gavi, the Vaccine Alliance (formerly Global Alliance for Vaccines and Immunisations)
GBS	Group B Streptococcus
GBS	Guillain-Barré Syndrome
HHS	U.S. Department of Health and Human Services
JPEG	Proposed WHO Joint Pregnancy Expert Group on Maternal Immunization
JTEG	WHO Joint Technical Expert Group (JTEG) on Malaria Vaccines in Pivotal Phase 3 Evaluation
LMIC	Low- and Middle-Income Countries
MDGs	Millennium Development Goals
MNCAH	Maternal, Newborn, Child, and Adolescent Health
MSF	Médecins Sans Frontières
NIH	U.S. National Institutes of Health
NITAG	National Immunization Technical Advisory Groups
NRA	National Regulatory Authority
ORWH	NIH Office of Research on Women's Health
PAHO	Pan American Health Organization
PANDRH	Pan American Pharmaceutical Regulation Harmonization Network
PASS	Post-Authorization Safety Studies
PPC	Preferred Product Characteristics
PREVENT	Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies
PRISM	Post-Licensure Rapid Immunization Safety Monitoring
R&D	Research and Development
RITAG	Regional Immunization Technical Advisory Groups
RSV	Respiratory Syncytial Virus
SAGE	WHO Strategic Advisory Group of Experts (SAGE) on Immunization
SDGs	Sustainable Development Goals
STAGE	Proposed WHO Strategic Technical Advisory Group of Experts on Maternal, Newborn, Child, and Adolescent Health
Tdap	Tetanus-diphtheria-acellular pertussis
TPP	Targeted Product Profile
UNICEF	United Nations Children's Fund
VAERS	U.S. Vaccine Adverse Event Reporting System
WHO	World Health Organization
YF	Yellow Fever
ZIKV	Zika Virus

EXECUTIVE SUMMARY

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.[i] 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.

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.

i 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.

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 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.

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

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.

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 or 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.

GUIDANCE

INTRODUCTION

This guidance addresses a critical gap in the global vaccine response to emerging and re-emerging pathogens—the needs of pregnant women and their offspring.

A century ago, the Spanish Influenza pandemic of 1918–1919 infected nearly a third of the world's population, killing between 50–100 million people.[1] In more recent years, Ebola, Lassa Fever, and Zika virus have devastated smaller populations. Each of these epidemics highlights the ways in which infectious disease outbreaks can severely, and at times uniquely, affect the health interests of pregnant women and their offspring.[i] In the case of influenza, Ebola, and Lassa Fever, pregnant women are at significantly higher risk of serious disease and death than the general population, with potentially devastating consequences for their offspring.[2,3,4] For example, Ebola infection in pregnancy not only poses severe maternal risk of death, but results in near 100% fetal demise or neonatal death.[3] Other pathogens that cause less severe disease in healthy adults can have significant associated risks for the developing fetus. In the wake of the 2016–2017 Zika virus epidemic, we now know all too well that even pathogens associated with mild illness in pregnant women can cause devastating congenital harms.[5,6] Regardless of whether a pathogen poses heightened risks of disease-associated harms in pregnancy, infection among pregnant women always has the potential to impact 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 for maternal immunization 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.[7,ii] 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, during numerous outbreaks and epidemics, pregnant women have been denied opportunities to receive vaccines that would have protected them and their offspring.

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.

i. 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.

ii. In recent years, there have been increasing efforts to develop select vaccines exclusively targeted to pregnant women to prevent illness in offspring, such as those against respiratory syncytial virus (RSV) and group B streptococcus. These candidate vaccines offer promise for the first set of vaccines specifically licensed for use in pregnancy. However, challenges still persist to ensure adequate inclusion of the interests of pregnant women in R&D agendas for vaccines targeted to the broader population.

This Guidance was developed to help advance these new approaches. It is the 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. The Guidance was also informed by broad consultation with a variety of external experts and stakeholders, as well as extensive reviews of the scientific literature and academic research on international ethics guidance and regulations regarding research with pregnant women. (See Appendix B for more details on our approach to the development of this Guidance.)

THE CONTEXT FOR THIS GUIDANCE

The Guidance was developed in the context of three significant shifts in bioethics and in vaccine science and practice that have the potential to advance the health interests of pregnant women and their offspring. The first is increasing global awareness that pregnant women have been treated inequitably in health research. The second is increasing global investment in routine maternal vaccination for endemic diseases. And the third is increasing global commitments to epidemic vaccine development and deployment.

There is growing recognition that the failure to attend fairly to the health interests of pregnant women in biomedical research is unacceptable. The World Health Organization (WHO), Pan American Health Organization (PAHO), Council for International Organizations of Medical Sciences (CIOMS), American College of Obstetrics and Gynecology (ACOG), and various U.S. federal agencies are advocating for the inclusion of the interests of pregnant women and their offspring in biomedical research, as are increasing numbers of bioethicists, including several bioethics scholars on our Working Group (see Preface).[8,9,10,11,12,13,14,15,16,17]

Through these significant advances in affirming the importance of involving pregnant women in research, four ethical principles have emerged and are presented in Appendix A. Our Guidance builds on these principles, as well as general principles of public health ethics, research ethics, and gender equity.

Also important to this Guidance are the substantial efforts currently being made to advance maternal immunization, which can protect mother and infant from endemic as well as epidemic diseases. These include efforts to: promote the use of existing vaccines, such as influenza and tetanus-diphtheria-acellular pertussis (Tdap) vaccines; develop new vaccines that are purpose-built for maternal immunization, such as those for respiratory syncytial virus and Group B streptococcus; and to harmonize the assessment of maternal, fetal, and neonatal health outcomes.[7,18,19,20,21,22] Depending upon the pathogen, these vaccines may prevent disease in the mother and fetus during pregnancy, and may also protect the newborn infant through passive transfer of maternal antibody. The development of our Guidance has benefitted from the work done to promote routine maternal immunization, and in turn, we anticipate that some of the recommendations we articulate in the context of maternal vaccination against emerging threats will also be applicable to routine maternal immunization efforts.

Another critical consideration for this Guidance is the increasing global commitment to the ethics of public health preparedness and response in epidemic contexts, and

the increasing global commitment to the development of vaccines to protect against emerging and re-emerging pathogens that threaten populations worldwide.[8,23,24,25,26,27] These include new funding mechanisms, research activities, and exploration of ways to streamline regulatory pathways and to address market disincentives. Notably, many of these global coordination activities have expressly included a commitment to equitable access, which the Coalition for Epidemic Preparedness Innovations (CEPI) has articulated as ensuring that *"the right vaccines are available when and where they are needed to end an outbreak or prevent an epidemic, that they are accessible to all people as necessary to achieve that objective…."*[25,28,29]

Global and local efforts have also focused on improving epidemic preparedness through strengthening health information systems, surveillance, and the infrastructure needed for detecting and responding to these health emergencies.

Collectively, these new efforts and investments present critical opportunities to better meet the needs of pregnant women and their offspring.

We recognize that it will not be easy to make the most of these opportunities. 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. Advancing justice 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.

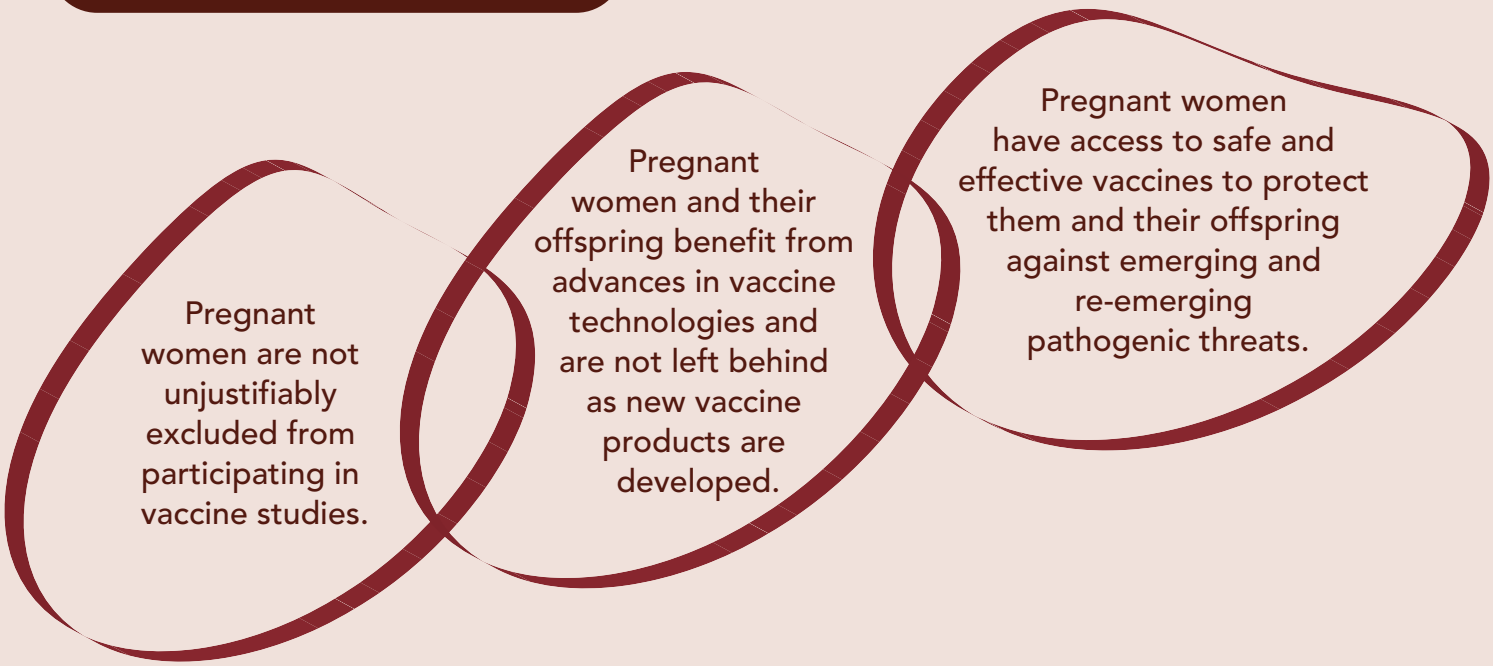
THE GUIDANCE

The Guidance begins by setting forth an aspirational vision and makes the case for its moral importance. We then specify 22 concrete recommendations, organized around three key areas: public health preparedness, R&D, and vaccine delivery.

The recommendations are 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, community advisory boards, and civil society organizations. Each recommendation specifies the actors to whom it is directed.

VISION

We envision a world in which:



When new or re-emerging pathogens threaten populations, one of the most often overlooked groups in the vaccine response is pregnant women. Historically, pregnant women and their offspring have been largely excluded from research agendas and investment strategies for vaccines against epidemic threats. They have also been excluded from the vast majority of vaccine research studies, including many with favorable risk-benefit profiles, with serious implications for their future access to safe and effective vaccines during outbreaks and epidemics.[30,31,iii]

Yet, pregnant women are no less susceptible than other populations to the harms of emerging infectious diseases. In fact, many emerging pathogens have more severe morbidity and mortality in pregnancy, including Lassa Fever, Ebola virus, pandemic influenza, and Hepatitis E virus. These and others, such as Zika virus, can also cause fetal loss and significant congenital abnormalities. Even when the harms of infection in pregnancy are similar to those in non-pregnant adults, infection during pregnancy can adversely affect two lives—the woman and her future child—not just one.

This state of affairs is profoundly unjust to pregnant women and their offspring, and deeply problematic from the standpoint of public health. When threatened by outbreaks or epidemics, pregnant women and their offspring are as entitled as any other population to protection of their

iii. Many co-authors of this guidance and others have published elsewhere on the multiple factors that have contributed to the widespread exclusion of pregnant women from biomedical research and the implications of these research gaps for appropriate management of the clinical needs of pregnant women. One notable exception occurred during the 2009 influenza pandemic, when H1N1 influenza vaccines were widely recommended and used during pregnancy, with accompanying prospective safety and immunogenicity studies. See Box 4 for more on the H1N1 vaccine and pregnancy.

health, and in many cases protection is best afforded by vaccination. The potential public health impact of excluding pregnant women from vaccination programs is substantial; each year, over 200 million women worldwide are pregnant.[32]

We envision a world in which pregnant women, like other population groups, have safe, effective, and accessible[iv] vaccines to protect them and their offspring against emerging and re-emerging pathogenic threats. To realize this vision, pregnant women will need to be on the agenda when decisions about investments and funding are made, and concerted efforts will need to be taken to gather sufficient evidence about the safety and efficacy in pregnancy of vaccine products and new vaccine technologies.

Several features of the current vaccine landscape work against the interests of pregnant women. Immunization options for pregnant women are currently viewed by many as severely limited, with only subunit or killed vaccines considered appropriate for use during pregnancy. Even if several candidates using these currently "acceptable" platforms are pursued for an emerging infectious disease, there are no guarantees that any will prove successful. Moreover, in an emerging epidemic, time matters. Subunit and killed vaccines often require multiple doses over time to induce protective immunity.

Live attenuated vaccines, by contrast, often require only a single dose to produce long-lasting immunity. However, live attenuated vaccines have historically been contraindicated for use in pregnancy or advised only in extreme epidemic or bioterrorism threat contexts. This is because of concerns about the theoretical risk that a vaccine virus which replicates systemically could cross the placenta to infect the fetus and produce adverse pregnancy and birth outcomes. For the large majority of live attenuated vaccines, adverse pregnancy, fetal, and neonatal outcomes have not been observed (see Box 12), yet there is still widespread reticence to use live attenuated vaccines in pregnancy and a continued preference for alternative vaccine platforms.

Novel vaccine technologies, such as nucleic acid-based and viral vector platforms, represent an increasing part of the vaccine R&D pipeline for emerging and re-emerging pathogens. These vaccine platforms may offer significant advantages over other more traditional platforms, particularly in the face of emerging outbreaks: they may be faster to develop, cheaper to manufacture, easier to store and transport, and hold the potential to stimulate broad and durable immunity. But little is known about their safety in pregnancy. If pregnant women are denied access to these and other novel vaccines because of insufficient evidence about safety, they may only have access to an inferior vaccine, or worse, to no vaccine at all.

From the standpoints of both equity and public health, this state of affairs is deeply problematic. Unless evidence is generated about the safety and efficacy of existing and new vaccine technologies, unfair and harmful differences in access to vaccines during public health emergencies between pregnant women and the rest of the population will only widen.

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iv. By "accessible" we adopt the "Five A's" conception of access introduced by Penchansky and Thomas in which access entails: availability, affordability, accessibility, acceptability/appropriateness, and accommodation, the latter regarding flexible arrangements for the timing and location of care provision that meet the circumstances of patients. Others have since added "sustainable" or "adequate supply" to this conception.

It is not just women who know they are pregnant, but all women of childbearing potential, who are disadvantaged by the absence of such evidence. During outbreaks and epidemics, vaccination campaigns will inevitably involve inadvertent exposures for women whose pregnancy status was unknown at the time of vaccination or who become pregnant within a relevant time window of vaccination. It is critical for women and their clinicians to have the best possible evidence to understand the implications of such exposures. Absent such evidence, pregnant women who are inadvertently exposed to a vaccine may experience unnecessary anxiety, both about potential harms to their offspring and also about whether they can expect the vaccine to protect them from disease.

Ensuring that pregnant women have safe, effective, and accessible vaccines to protect them and their offspring during outbreaks and epidemics will require the generation of evidence from pregnant women participating in vaccine research. Research with pregnant women is morally and technically complex. But as we noted in the Introduction, there is increasing recognition that research with pregnant women can be conducted in ethically, scientifically, and medically responsible ways, and indeed that there is an ethical and public health imperative to do so. So long as vaccine studies with pregnant women are not conducted, the evidence needed to ensure that pregnant women have access to vaccines in public health emergencies cannot be generated.

Moreover, the exclusion of pregnant women from vaccine trials conducted in the midst of an imminent threat may unjustifiably deny them what may be the only or best way to protect themselves and their offspring from that threat.[30] The more dangerous the pathogen, the more important it is to afford fair opportunity to participate in research and ensure access to the potential benefit it may bring.

In the recommendations that follow, we lay out a path toward the realization of our vision of a world in which pregnant women and their offspring will benefit from the best possible vaccines against emerging and re-emerging pathogens; a world in which pregnant women are treated fairly and respectfully; and preventable harms to them and to their offspring are safely averted. The recommendations fall under three key areas: I) Preparedness: activities that should be undertaken as part of public health preparedness in anticipation of outbreaks; II) R&D: appropriate inclusion of the interests of pregnant women and their offspring in research and development of vaccines against emerging epidemic threats; and III) Vaccine Delivery: ensuring that pregnant women are appropriately included in vaccine campaigns during active outbreaks and epidemics.

RECOMMENDATIONS

I. 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; 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

Reliable health information systems and reliable surveillance systems are both essential for an appropriate and rapid response to emerging pathogenic threats. As countries and partners continue to invest in strengthening these systems, relevant indicators of maternal, obstetric, and newborn outcomes must be captured in each system. As noted in the WHO Guidance for Managing Ethical Issues in Infectious Disease Outbreaks, it is critical to collect information about these indicators to assess potential differences in the risk of infection, modes of transmission, outcomes, and response to interventions.[8] It is equally critical that these systems are integrated with bi-directional communication of data and signals. Unless these systems can and do effectively "talk" to each other, preventable harms to pregnant women and their offspring are likely to occur.

Collecting data on maternal, obstetric, and newborn health can advance the interests of pregnant women and their offspring in at least three ways. First, having baseline rates of specific outcomes in pregnancy and the post-partum period can enable detection of significant increases in adverse maternal, fetal, or newborn events that may signal the presence of infectious disease threats as a possible causal factor. This capacity is especially important for pathogens associated with unique or severe manifestations in pregnancy. For instance, significant increases in certain congenital malformations like microcephaly could signal the presence of circulating Zika virus.

Second, when surveillance activities have already detected a circulating pathogen in the population, baseline data on maternal, obstetric, and newborn health can help determine whether the pathogen is causing additional or more severe pregnancy-specific harms—but only if infectious disease surveillance systems also capture relevant indicators. If information is not collected on pregnancy status or pregnancy outcomes in surveillance case reports, it will be difficult if not impossible to assess differential morbidity and mortality among pregnant women or differential fetal impacts. For instance, the lack of pregnancy-specific data captured in Ebola surveillance efforts presented challenges to the accurate assessment of the burden of Ebola virus disease in pregnancy.[33,34]

Third, having background rates of maternal, pregnancy, and neonatal outcomes can help in assessing potential risk relationships between vaccination and adverse events. Without reliable background rates, it will be difficult to interpret potential safety signals

in a vaccine trial or in a vaccine program, and thus difficult to determine whether there is sufficient reason to caution against the use of the vaccine in pregnancy. Based on an event that might be unrelated to vaccination but relatively common in pregnancy (e.g., early pregnancy loss), pregnant women who would otherwise be trial participants could be excluded, perhaps without justification, and women who become pregnant during a trial would likely be removed from the study, after which they might experience substantial unwarranted anxiety, in some cases leading them to terminate a pregnancy from fear of harm. Moreover, if the vaccine trial is successful and the vaccine is deployed against a looming outbreak or epidemic, pregnant women and their offspring could be denied the benefits of vaccine protection based upon false safety signals. Similarly, if pregnant women are offered vaccine during an outbreak or epidemic and adverse events in pregnancy begin to be reported, the inability to interpret the clinical significance of these events could result in a situation in which pregnant women unnecessarily forego and are advised against beneficial immunizations out of unsubstantiated fears of vaccine-associated harms.[35,36]

Coordination and integration between the systems capturing adverse pregnancy and birth outcomes and those assessing pathogenic threats can also be helpful in weighing the relative risks of potential congenital harms related to vaccination and those related to infection with the circulating pathogen.[37,38,39,40] When little is known about a pathogen's effects in pregnancy, additional case series and prospective cohort studies may be critically important not only for identifying the particular ways in which the disease presents, but to establish clear and harmonized case definitions for ongoing surveillance efforts. For example, since the onset of the Zika epidemic in Latin America, targeted epidemiologic studies have led to refinement and expansion of the case definition for congenital Zika syndrome.[6,41]

Box 1: Challenges and Opportunities Associated with Collecting Background Rates

There are many challenges to collecting data on important pregnancy-related indicators, including: conflicting, non-standardized definitions of adverse obstetric and neonatal events; differential capacities of national or subnational health systems to detect prevalence of pregnancy-related conditions; and variability in the prevalence of these events across different populations. Rates of adverse outcomes may also vary across gestation—a detail which may not be captured by routine information systems—and increasing use of ultrasonography may lead to higher rates of detection of pregnancies and of fetal anomalies. Increased use of ultrasonography may also allow for more frequent assessment of gestational age, which is critical for the accurate evaluation of many adverse birth outcomes. An increasing focus on expanding access to antenatal care (ANC) will likely lead to an increased detection of obstetric events, particularly as the emphasis is on expanding such care to underserved populations.

Rates of adverse obstetric and neonatal outcomes should be contextualized by accessibility and uptake of antenatal care, skilled birth attendance, and other indicators recognized to improve these outcomes. Among the more challenging yet important data to obtain relates to indicators around pregnancy loss (also called miscarriage, spontaneous abortion, and stillbirth). Of note, pregnancy loss in the first trimester is more common than later loss: it is estimated that 80% of pregnancy loss occurs in the first trimester.[42,43] Yet many early losses are neither recognized nor reported. The results of several studies and reviews converge at a rate of early pregnancy loss among clinically recognized pregnancies ranging from 15–20%.[44,45] However, continued surveillance and refinement of these data are important.

Given these challenges (see Box 1), background rates must be used with care and should account for the uncertainty in such estimates, including differences in geography, season, ethnicity, maternal age, and week of gestation, as well as the limitations of the methods used to determine these rates.[35]

There are also new opportunities to strengthen these data collection efforts. Because of the ongoing focus on improving maternal and infant outcomes in many countries, including in pursuit of the Millennium Development Goals (MDGs 4&5) and the Sustainable Development Goals (SDGs), there have already been investments made to capture some of these data.[47] For example, the Global Network for Women's and Children's Health Research launched a prospective, population-based registry of pregnancies across 7 low- and middle-income country (LMIC) sites to establish better reporting systems on important pregnancy and perinatal health indicators.[48] Significant efforts have been made on behalf of the Brighton Collaboration and others to harmonize case definitions of obstetric and neonatal events that could occur in immunization in pregnancy and/or maternal and child health studies and programs.[49] Additionally, mHealth technologies and other relevant apps should be used as needed in systematic data collection efforts. For example, the U.S. National Institutes of Health (NIH) launched a crowdsourcing platform called "Pregsource." (https://pregsource.nih.gov)

Some important indicators:

Pregnancy and birth outcomes (rates)

- Spontaneous abortion or miscarriage
- Stillbirth
- Pre-term birth
- Low birthweight
- Congenital abnormalities
- Neonatal mortality

Maternal health outcomes (rates)

- Maternal mortality
- Pre-term labor and pre-term premature rupture of membranes
- Adverse obstetric events/conditions, including: hyperemesis, chronic hypertension, gestational hypertension, gestational diabetes, pre-eclampsia, eclampsia, infection such as urinary or upper respiratory infection, chorioamnionitis, puerperal infection, bleeding and clotting disorders, pulmonary embolus, and cardiovascular morbidity such as peripartum cardiomyopathy.[46]

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. Much has been written about how inadequate vaccine confidence leads to suboptimal uptake of safe and effective vaccines.[50,51,52] The challenges associated with vaccine confidence can be especially pronounced among pregnant women and their providers, given concerns and mixed messaging about potential fetal harms, the limited data available regarding safety and immunogenicity of vaccines in pregnancy, and the well-characterized phenomenon of risk distortion in pregnancy.[50,53,54] Uptake of widely recommended maternal immunizations has been far below ideal in both high- and low-income country contexts.[53,55,56,57,58]

Unless vaccine confidence among pregnant women and the health professionals who care for them is enhanced, these suboptimal coverage rates will continue. Action is needed now, in advance of any public health emergency, to develop and implement evidence-based strategies to increase professional, community, and individual confidence in vaccination during pregnancy in the specific context of outbreaks and epidemics.[8]

Where possible, these efforts should both leverage and contribute to ongoing efforts in the context of routine maternal immunization, as it is likely that the drivers of vaccine confidence are similar. WHO and PATH, with support from the Gates Foundation and CDC, have already begun to develop resources and guidance on promoting vaccine confidence among pregnant women, with a focus on introducing maternal influenza vaccine in low- and middle-income countries and on planning for introduction of maternal vaccines in late stage clinical development.[59] Available resources include a sample protocol for assessing awareness and acceptance of maternal influenza vaccination among health care workers, women of childbearing potential, and their spouses.[60] Other examples of resources include a regional field guide for maternal and neonatal immunization developed by PAHO and immunization communications toolkits for providers developed by ACOG.[61,62] These resources need to be adapted and expanded upon to address the specific context of outbreaks and epidemics.

Developing and implementing evidence-based strategies will require sustained engagement with pregnant women, their health professionals, and other stakeholders. It will also require an investment in empirical social science research to better understand the drivers of vaccine confidence in different cultural settings in the specific context of pregnancy, outbreaks, and epidemics, as well as the resources to implement and evaluate evidence-based interventions that are grounded in this research.

Box 2: Determinants of Vaccine Hesitancy/Confidence

There are many drivers of vaccine confidence in general and in pregnancy more specifically. The WHO SAGE Vaccine Hesitancy Working Group developed a model of determinants of "vaccine hesitancy" that was structured around three domains: (1) contextual influences—including the roles of religion, culture, gender, and the media environment; (2) individual and group influences—including personal perceptions of vaccine risks and benefits, experiences and interactions with health providers, and influences of family members and peers; and, (3) vaccine and vaccination-specific issues—which entail specific aspects related to characteristics of a vaccine and how it is delivered.[50,51]

RECOMMENDATION 3

Communication plans should be developed for clear, balanced, and contextualized dissemination of vaccine study findings, recommendations for 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

Communication about specific vaccines, their associated risks and benefits, and recommendations for their use is critical to an effective outbreak or epidemic response. Nowhere is this more true than in pregnancy, where risk distortion is a prominent feature of both professional and personal risk assessment.[44,63,64] Several strategic risk communication resources for vaccines already exist and, with adaptation, they can be helpful in improving communication to mitigate against these pregnancy-specific concerns.[65,66,67,68,69] Below, we discuss some pregnancy-specific communication strategies that should be developed for three distinct contexts.

Communicating About Vaccine Trials and Research Findings

The need for effective and contextualized communication begins with early evidence generated in non-clinical studies and clinical trials. This includes findings from vaccine studies enrolling pregnant women, vaccine studies with women of childbearing potential that may have unintended vaccine administrations in pregnancy, as well as developmental toxicology studies using various animal models. Because of the likely public interest in any clinically relevant signals and findings on vaccine safety and efficacy in pregnancy, effective and timely communication to regulatory authorities, policymakers, and health care providers, though critical, is insufficient. Plans must also be developed for effective communication to the public, including with and through traditional and social media (see Box 3).[70] The communication plan should include any findings suggestive of efficacy and safety in pregnancy. It should also ensure that findings of adverse events are contextualized by background rates for these outcomes, as well as by the potential harms of infection to pregnant women and their offspring. Communications should also be transparent about the evidence available

regarding use of a particular vaccine in pregnancy, given that decisions about use may need to be made relatively early in the clinical development process.[54, 68, 69]

Communicating Vaccine Recommendations in Pregnancy

During outbreaks and epidemics, public health authorities, recommending bodies, and professional associations will be determining whether a vaccine should be offered during pregnancy, and if so, whether the recommendation is specific to pregnancy trimester. Those making this determination should communicate the recommendation and the reasons behind it as clearly as possible to health care providers, affected communities, and pregnant women.[8]

If the recommendation is that pregnant women are offered the vaccine, the communication plan must be clear about the benefits of vaccination, any known risks to pregnant women and their offspring, and why the anticipated benefits outweigh these risks. In explaining why the vaccine is recommended for use in pregnancy, the communication plan should be sensitive to issues of low vaccine confidence among pregnant women and the communities in which they live, as well as public anxieties surrounding outbreaks and epidemics. The communication plan should also be sensitive to the critical role that health care providers can play in increasing the likelihood of vaccine acceptance.[71,72] Health care providers vary in knowledge and attitudes about vaccination in pregnancy. Discrepancies often exist between health care providers' awareness of vaccine recommendations and their adherence to them.[73,v]

If the recommendation is for pregnant women not to be offered access to a vaccine, the communication plan should be sensitive to fears and concerns about the pathogenic threat that pregnant women share with the rest of the population, and include information about what alternatives, if any, are available to pregnant women who must now face the outbreak or epidemic without benefit of a vaccine to protect them and their offspring.

Communication plans should also anticipate the likelihood of unintended exposures during pregnancy for any vaccine offered to women of childbearing potential. Information should be provided on available evidence about potential risks of pregnancy exposure. This will help pregnant women and their clinicians make more informed decisions about clinical management options.

Communicating Adverse Events in Pregnancy during Outbreak Response

When pregnant women are included in a vaccine response to an outbreak or epidemic, the communication plan for the vaccine campaign should anticipate the prospect that pregnancy-related adverse events will be suspected over the course of the campaign. It is possible that an adverse event may be the result of vaccine administration. However, as discussed in Recommendation 1, many things can go wrong over the course of pregnancy into early infancy, and some may be inappropriately attributed to the vaccine. The mishandling of risk communication of suspected pregnancy-specific adverse events during an outbreak or epidemic can lead to significant harms to pregnant women and their offspring, including women choosing to forego use of beneficial vaccines or

v. For licensed vaccines, there are now new mechanisms in place to include more nuanced and contextualized evidence and recommendations about vaccine use in pregnancy on product labels and package inserts, in particular under the Pregnancy and Lactation Labeling Rule of the FDA.

unnecessarily seeking to terminate wanted pregnancies.[74] Therefore, a critical best practice for communicating pregnancy-specific vaccine findings is to ensure that any reports of adverse pregnancy or birth outcomes occurring during the epidemic response are interpreted in light of the best available information about baseline rates of adverse obstetric and neonatal events, and should include an acknowledgement that a high percentage of adverse events in pregnancy have no known cause. Additionally, any findings should be presented in conjunction with the type, severity, and frequency of adverse obstetric and neonatal events known to be caused by infection with the wild-type pathogen.

Box 3: Communicating with and through the Media

Engagement with traditional and new media is necessary in advance of and during outbreaks. Media play a critical role in providing the public with real-time information about the epidemic and response and also often report research findings as well. Risk communication planning may include table-top exercises to train reporters, editors, and publishers about background rates of adverse obstetric and neonatal events to mitigate sensationalist stories and avoid false attribution of adverse events to vaccine use. This strategy was successfully implemented in the campaign to vaccinate pregnant women during the 2009 H1N1 pandemic in the U.S. by the National Vaccine Program Office.

Box 4: Pregnant Women and Influenza Immunization

Pregnant women are considered a priority population for influenza vaccination because they and their offspring are at increased risk of complications from influenza, including serious illness and death. Yet despite longstanding recommendations for routine influenza vaccination in pregnancy, immunization coverage remains low among pregnant women. During the recent 2017–2018 influenza season, only 35.6% of pregnant women in the U.S. had received the flu vaccine as of November 2017—a significant drop from previous years where coverage was closer to 50%.[55,75,76] Although it is difficult to pinpoint the specific causes of lower influenza vaccine uptake in 2017, one contributing factor may have been a 2017 study highlighting a possible association between miscarriage and influenza vaccines—and the media response to the release of these findings.[77,78,79] ACOG and the CDC promptly released statements about the limitations of the study and reaffirmed the continued public health and clinical importance of influenza vaccination in pregnancy, but headlines about the possible "link" to miscarriage gave rise to public concern.[80,81,82] This example highlights the challenges of effectively communicating new findings that signal potential vaccine-associated risks pregnancy, the central role of the media as an information broker to the public, and the limitations of current practices for messaging to the public about recommended uptake of vaccines in pregnancy. More work is needed to determine optimal modes and platforms for professional organizations and the mainstream media to responsibly and effectively communicate around the risk of vaccine use in pregnancy to providers and pregnant women.

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

There are currently a number of efforts underway to advance our scientific understanding of the human immune system to develop better, rationally designed vaccines and biologics. Because pregnancy can alter the 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 appropriate for use in pregnancy. For example, the Human Vaccines Project has launched the Rules of Immunogenicity Program to examine the underlying mechanisms required to generate appropriate and durable immune responses against infectious diseases and cancer across the age spectrum and in diverse populations.[83] This project presents an important opportunity to explore how and why vaccines may work differently in pregnancy.

Additionally, more work is needed to understand the specific dynamics of immune cell interactions at the maternal-fetal interface. Notably, the NIH issued a funding announcement in June 2018 calling for proposals that identify and define immune mechanisms during normal pregnancy and explore the mechanisms of immune responses triggered by infections or vaccination during pregnancy.[84] We hope that this and other funding support will stimulate further research in this space.

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 CEPI

Vaccine research, development, and deployment take place against the backdrop of the legal and financial interests of vaccine developers and manufacturers. Vaccine developers and manufacturers already face significant market challenges and uncertainties in pursuing products targeting emerging and re-emerging pathogens.[26] 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.[85]

Some mechanisms are currently in place in certain settings to encourage development of beneficial biomedical products that are unlikely to generate a profit, and other programs protect against liability concerns when products are used in certain contexts, like public health emergencies, or by certain special populations, like children. These and new incentive programs need to be intentionally inclusive of the needs and interests of pregnant women.

Following the Ebola crisis of 2014, calls for a global vaccine fund led to the creation of CEPI

to stimulate, facilitate, and finance vaccine development against emerging pathogenic threats—many of which would be unlikely to be pursued based on market incentives alone.[26,86] Given CEPI's central focus on de-risking the vaccine development space for emerging infectious diseases and their commitment to working with industry, regulators, and other bodies to get vaccines developed, authorized, and delivered to the people who need them, CEPI can play a pivotal role in ensuring that pregnant women and their offspring fairly benefit alongside other populations from these efforts and investments.

Other mechanisms with proven international success in incentivizing product development exist (see Box 5). Some may have the potential to lower development costs, increase financial sustainability, and cultivate early brand recognition and allegiance, ultimately benefiting market share and encouraging product development for those in need.[87,88] As these mechanisms are explored and leveraged to promote the development of vaccines against emerging pathogens, special attention should be offered to products that will be suitable for use in pregnancy.

At the same time, it will be critical to address disincentives concerning the legal and financial risks of administering vaccines during pregnancy. In the context of vaccine research studies, 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. Some existing programs established for the U.S. by the Public Readiness and Emergency Preparedness Act protect individuals and entities from liability claims when covered vaccines are administered during research trials or through emergency response efforts.[89,90] This Act also established the Countermeasures Injury Compensation Program, which compensates any individuals—including pregnant women and offspring who were *in utero* at the time of vaccine administration—who suffer specified, serious physical injuries from receiving covered vaccines.

Box 5: 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

In recent years, there have been calls to establish a global vaccine injury compensation system to combat "the specter of vaccine injury"—stating in particular the impact that compensation programs may have on vaccine development in the context of public health emergencies.[91,92] Beyond the benefits associated with mitigating liability concerns, scholars have noted that no-fault compensation systems for adverse events attributable to vaccinations offer further intrinsic and instrumental value: (1) they offer compensation to those who suffered vaccine-associated injuries; (2) they may address inequities inherent to vaccine-injury compensation mechanisms that rely on

litigation (particularly when many affected have few resources to pursue legal suits); and (3) the public health literature strongly suggests that no-fault compensation systems increase public confidence in vaccination.[93] 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.[vii] (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.[vii]

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

Preparedness

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.

Immunization and the proposed Strategic and Technical Advisory Group (STAGE) on Maternal Health.[viii]

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.

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.

II. RESEARCH & DEVELOPMENT OF VACCINES AGAINST EMERGING PATHOGENIC THREATS

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

The organizations shaping and investing in the vaccine pipeline against emerging pathogenic threats have the opportunity to ensure that, among the candidates that are prioritized for development, there are at least some that use platforms and adjuvants that are most likely to make them suitable for use during pregnancy. Early investment in options that are most likely to be acceptable during 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 from emerging infectious diseases.

For pathogens that pose significantly higher threats in pregnancy—of fetal harm, maternal harm, or as is often the case, both—funding calls should designate greater investment priority to candidates likely to be suitable for use during pregnancy. When pregnant women or their offspring are at higher risk of harm from the pathogen, it would be particularly unjust for their needs not to be included in vaccine development priorities. Moreover, because the business case for developing vaccines for outbreak diseases is often weak, much of the investment in vaccine R&D comes from public funding sources. The large role for public financing underscores the justice claims of pregnant women to have their needs fairly included in societal investments in vaccine development.

Funding agencies also have the responsibility to help ensure that pregnant women will not be left behind as vaccine technology advances. Novel vaccine technologies, such as nucleic acid and viral vector platforms, represent an increasingly important part of the vaccine R&D pipeline for emerging and re-emerging pathogens. However, little is known about their safety in pregnancy, although there is optimism about their use in pregnant women.[94,ix] Funders who are supporting the development of vaccines for emerging pathogens that rely on novel technologies should require and fund research activities to help fill this gap, including timely developmental toxicology studies for vaccine candidates demonstrating promise in phase 1 studies, studies of immune response in pregnancy, and the inclusion of pregnant women in pre- and post-market research when ethically and legally permissible. (See Recommendations 9, 10, and 11.)

As noted earlier, there has been a dramatic shift toward proactive investment in the development of vaccines against emerging pathogens since the 2014 Ebola crisis, as part of larger efforts to strengthen epidemic preparedness. Emblematic of this shift is the launch of CEPI, a partnership between public, private, philanthropic, and civil society organizations that is supporting the development of several promising vaccine candidates against priority pathogens ahead of outbreaks. There are also a range of WHO

ix. "…the ideal vaccine will be based on a non-replicating platform that is safe for use during pregnancy. These platforms include inactivated whole virus, subunit, or mRNA-based or DNA-based vaccines that express selected viral proteins." In Poland et. al., 2018.

activities designed to better coordinate global research efforts that should be leveraged to appropriately address the interests of pregnant women and their offspring in vaccine R&D. These include the WHO R&D Blueprint and Roadmaps, as well as Target Product Profiles (TPPs) and Preferred Product Characteristics (PPCs) for vaccines being developed against specific pathogens. Collectively, these documents highlight the broad priorities for preparedness and response and signal the target populations and product characteristics that academic and commercial researchers should pursue when developing interventions. For pathogens that pose significantly higher threats in pregnancy, pregnant women should be included among the target populations, and one or more vaccines that are suitable for use in pregnancy should be included among the types of vaccines targeted for development.

It will ultimately fall to researchers and funders to prioritize developing vaccine candidates with acceptable characteristics for use in pregnancy. When reviewing proposals, funding agencies such as CEPI, BARDA, NIH, the European Commission, the International Vaccine Initiative, and others should strongly consider the likely acceptability for use during pregnancy of each vaccine candidate, alongside the other review criteria, and include some candidates that are likely to be suitable for use during pregnancy as part of the overall portfolio of funded proposals. It is worth emphasizing that many products developed with the intent to be safe and effective in pregnancy are likely to be safe and effective in other affected populations and can be widely deployed.

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 and sponsors; vaccine developers

It is possible that the vaccine candidates that move most rapidly through the R&D pipeline turn out to be problematic for use in pregnancy, even when a concerted effort in investment and funding decisions has been made upstream to keep this from happening. For example, as a candidate advances through various stages of clinical development, an otherwise promising vaccine may produce high fever in some research participants, raising concerns about its use in pregnancy because of documented associations between high fever in pregnancy and congenital malformations.[95,96,97] 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 problematic from both a public health and ethics perspective, and is particularly dire when the target pathogen has more severe consequences in pregnancy. When pregnant women and their offspring suffer more than other population groups from the emerging infectious disease threat, justice calls for the vaccine enterprise to make every reasonable effort to bring to market a product pregnant women can safely and effectively use. Consider, for example, the case of Zika virus (ZIKV), where the most devastating effects of

the virus are caused by infection in pregnancy. If the only promising candidate to advance to phase 3 trials were a live-attenuated ZIKV vaccine, pregnant women might be left behind, even though their offspring are most at risk for harm from ZIKV. In this case, because there is a theoretical risk of the live-attenuated vaccine causing the very condition it seeks to avert,[x] investing in the development of candidates that do not entail this risk is critical to ensuring that pregnant women have an available option to safeguard their fetuses and themselves in the event of future ZIKV outbreaks.

ZIKV is not the only emerging or re-emerging pathogen where pregnant women and their offspring face higher risks than other affected populations. Consider another WHO priority pathogen, Lassa Fever virus, where a vaccine option for pregnant women is critically important. Documented mortality rates for hospitalized patients with Lassa Fever have typically ranged between 15–20% (with some instances of mortality over 50%), but for women in their third trimester of pregnancy, mortality rates climb to 80–90%.[98,99,100] Not only is the risk of death significantly higher in pregnancy, but ribavirin, the primary treatment for Lassa Fever, is contraindicated for use in pregnancy due to suspected associations with birth defects.[101,xi] Many of the vaccine candidates under development for Lassa Fever employ novel vaccine platforms or replication-competent viral vectors, including two platforms that have recently received CEPI funding.[102] If early safety data do not support evaluation of these vaccines in pregnant women, or their use in pregnant women during an outbreak, then additional vaccine candidates should be developed.

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

Under the new preparedness frameworks noted above, organizations like CEPI have committed to supporting "just-in-case" vaccine development, from pre-clinical stages through phase 2 clinical studies, so that promising candidates can be quickly evaluated in large-scale trials during outbreaks.[103] As a matter of equity, pregnant women should be able to participate in these studies when appropriate vaccine candidates are identified and the likely benefits of participation outweigh the risks (see Recommendation 11). However, current regulatory guidance requires that certain non-clinical studies, such as developmental toxicology studies in animals, must be completed prior to including pregnant women in clinical trials.[104,105,106,107]

x. Live-attenuated vaccines have usually been contraindicated in pregnancy, though not always, as evidenced by Yellow Fever vaccine, which is recommended for use in pregnancy where Yellow Fever exposure is possible. Contraindications have received special weight where the vaccine is derived from a replicating virus that has known associations with congenital malformations (e.g., Rubella). Although no observed cases of vaccine-associated congenital rubella syndrome have been documented, the vaccine remains contraindicated in pregnancy, though recent recommendations emphasize that inadvertent exposure should not prompt discussions of pregnancy termination (e.g., CDC Guidelines for Vaccinating Pregnant Women). Further, there is widespread reticence among providers generally to use live vaccines, whether or not the wild-type virus is associated with congenital defects (see Box 12). In the case of ZIKV, there would have to be significant efforts to establish the safety profile of a live-attenuated ZIKV vaccine in pregnancy, and many experts agree it is unlikely that adequate evidence would be gathered that would lead to a recommendation for use in pregnancy.

xi. The contraindication for ribavirin in pregnancy is currently based on an animal model that found signals of teratogenicity. There are pregnancy registries collecting data on possible effects of in-utero exposures to ribavirin, and while they have yet to find signals of associated birth defects in humans, the sample size is still to small to be conclusive (Sinclair SM, et al. 2017).

For this reason, required non-clinical studies for evaluation in pregnant women should be conducted while promising vaccines move through phase 1 and 2 clinical trials, so that these vaccines could be offered without delay to pregnant women during an outbreak, whether in research or deployment. While not all vaccine candidates will successfully advance through clinical trials, plans should be made at the outset, and funding secured, to allow timely non-clinical evaluations for appropriate vaccine candidates.

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.[108,109] Immunogenicity studies would be particularly valuable if a correlate of protection for the vaccine has already been established. These studies would also provide opportunities to gather additional safety data for these vaccines in pregnancy.

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 occurrence of an outbreak 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. The example in Box 7 provides an illustration of such an instance.

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 who may be affected by outbreaks and epidemics, as a class. The second concerns individual pregnant women who live in areas where trials are being conducted amid outbreaks.

Box 7: Novel Yellow Fever Vaccines and Immunogenicity Studies Absent an Outbreak

Consider the case of a new Yellow Fever (YF) vaccine candidate that employs a platform that is not replication-competent—compared with the current live-attenuated YF vaccine that has been in use since the 1930s. The current vaccine is quite effective at inducing long-lasting immunity. However, there has been recent interest in pursuing new YF vaccines because of concerns about rare but serious adverse events in the general population associated with the current product, as well as additional precautions regarding the use of the live-attenuated vaccine in young infants, the elderly, immuno-compromised people, and pregnant and lactating women.[110] New YF vaccine candidates using inactivated virus and nucleic acid platforms may have better safety profiles;[108,111,112,113,114] moreover, recent supply issues underscore the potential advantage of novel vaccines that can be rapidly manufactured to better meet demand, particularly during public health emergencies and pandemics.[115,116,117,118]

If a new YF vaccine candidate stimulated sufficient protective immunity in healthy, non-pregnant adults, and evidence suggested that the safety profile of the new candidate for pregnant women was better than the current live-attenuated vaccine, it would be important to conduct further studies assessing the immune response of this new vaccine among pregnant women. As some studies suggest that immune responses in pregnancy to the current YF vaccine may be impaired, it would be critical to determine whether the new vaccine would be sufficiently protective in pregnant women compared with their non-pregnant counterparts.[108,119] Because there are established correlates of protection for YF vaccines, immunological bridging studies in pregnant women could be conducted. Also, for pregnant women living in communities where YF is a recurrent threat, the benefits of receiving the experimental vaccine, which include not needing to be exposed to the current vaccine, would likely outweigh the risks. This is just one hypothetical example to illustrate a case in which it would be scientifically and morally important and appropriate to assess immune response in pregnancy between or ahead of potential exposures.

Pregnant Women as a Class

As we have noted throughout, the distinct physiology of pregnancy, together with concerns about fetal effects, limits the extent to which evidence from non-pregnant adults can establish an adequate evidence base for vaccine use during pregnancy. Because of reasonable constraints on sample size and length of follow-up, it is likely not possible to generate the same level of evidence about efficacy and safety for pregnant women and their offspring as for the general population.

That said, 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 as the evidence for the general population. This requires development of an evidence base that includes data obtained directly from pregnant women.

For many pathogenic threats, including those that emerge only intermittently, outbreaks may be the only time in which it is possible to generate critical pieces of evidence on

investigational vaccines in pregnancy. Alternative strategies to generate evidence on vaccines during non-outbreak periods, such as phase 1–2 studies or human challenge trials, have ethical and regulatory constraints limiting the involvement of pregnant women, particularly where they offer no prospect for direct benefit.

At minimum, sufficient numbers of pregnant women should be recruited in vaccine efficacy trials during outbreaks to allow an assessment of immunogenicity and to gather as much evidence as possible about safety. Clinical development plans and study protocols may adopt a range of approaches for collecting data from pregnant women, including the conduct of parallel or companion studies to the main efficacy trial or through a sub-study of the main trial.

While data collected from pregnant women may not be analyzed with data from the main trial, investigators should integrate analysis of data collected from pregnant women with data from participants in the main efficacy trial who become pregnant (see Recommendation 12), including information regarding relevant differences in week of gestation at time(s) of administration(s).

Pregnant Women as Individuals

There is a second, independent reason motivated by justice as to why pregnant women should have opportunities to participate in efficacy studies of vaccines conducted in outbreak settings. As the moral equals of others, pregnant women should have fair access to the prospect of direct benefit that may come from receiving an experimental vaccine.[8]

The principle of fair access to research participation is a key and independent pillar of research ethics. When research offers participants the prospect of direct benefit, this principle requires that those who could benefit from inclusion and otherwise meet general criteria of scientific relevance and regulatory protection be afforded the opportunity to enroll. This applies to pregnant women no less than to other potential research subjects. Indeed, for pregnant women, the benefits of research participation may be especially high. Pregnancy can make a woman more susceptible to infection and exacerbate the risks associated with some pathogens; and benefits may accrue to two entities, the woman and her future child. Like all potential research participants, pregnant women may differ in their interest in participating in a vaccine

Box 8: Randomization of Pregnant Women in Vaccine Studies

There may be cases in which prospectively enrolled pregnant women should not be randomized, even if randomization is acceptable for the main study population. For example, when the probability and severity of harms associated with infection are significantly greater in pregnancy compared with other affected populations, with few available alternatives, and the vaccine shows promise for immunological protection, it may be unethical to assign pregnant participants to anything but the investigational vaccine. Another reason why it may be appropriate to assign all pregnant participants to receive the investigations vaccine is that projected sample sizes for pregnant women may not be large enough to detect statistically significant differences between a control group and an intervention group.

study. That said, they should be afforded a fair opportunity to protect themselves and their offspring from the circulating pathogen through research participation that is comparable to the chance available to members of other affected groups.

When the clinical development plan does not include studies with pregnant women during outbreaks, despite a prospect of net benefit from their participation, a double injustice results. The claim of pregnant women to an evidence base appropriate to their needs is denied, and the claim of individual pregnant women to fair access to participate in studies of the investigational vaccine is also denied. The best outcome in this circumstance is for the clinical development plan to be amended and resources secured to initiate studies with pregnant women as quickly as possible. ***Those responsible for clinical development plans that offer no opportunity for pregnant women to enroll in vaccine efficacy studies conducted during outbreaks must provide sufficient and scientifically valid justification for excluding pregnant women from this research (see Box 9).*** When pathogenic threats are particularly serious, or when pregnant women and their offspring face the most severe harms of infection, it may be very difficult to ethically justify their exclusion from vaccine studies.

Box 9: Fair Access to Trials with the Prospect of Direct Benefit

Fair access to research is not equivalent to automatic access. Instead, it means that restricting eligibility based on a given condition or demographic profile must be based on acceptable justification for exclusion. Reasons that are not considered acceptable bases for exclusion from research involving prospect of direct benefit include logistical costs; liability issues; that some people would be more costly to recruit, retain, or responsibly care for or oversee; or past practices of exclusion. Reasons that are considered acceptable include an individual not meeting criteria of scientific relevance or not meeting standards of acceptable research-related risk. In between are reasons of scientific complexity or risks to ongoing research. Whether or not these reasons justify exclusion in a given instance will depend on the importance of the research, the potential for adjusting the research design in ways that will allow inclusion, and the degree of prospective benefit of participation to the individuals who would be excluded. In general, the stronger the potential net benefit of participation and, more specifically, the stronger the benefit to those who would be excluded relative to other potential participants, the higher the burden of justification for exclusion.

Standards and Resources for Inclusion of Pregnant Women in Research

For both sets of reasons outlined above, it is critical that vaccine research conducted during outbreaks include appropriate plans for research with pregnant women whenever the research meets ethical standards for permissible enrollment of this population. These standards generally consider pregnant women eligible for enrollment in research involving medical interventions if the risk to the fetus is minimal or, as is more likely here, when there is a reasonable judgment that the prospective benefits of enrollment outweigh the risks, and that research participation has the prospect of being at least as net beneficial as alternatives to participation.

These ethical standards are reflected in many regulations governing research with human subjects (see Appendix A). Should the jurisdiction in which research is to be conducted have regulations that would not permit research with pregnant women even when the likely benefits outweigh the risks, sponsors and investigators will have to abide by these requirements. However, they should make efforts to persuade regulators to change the regulations or to make an exception in view of the public health and equity interests that are at stake.

For vaccine research, determining whether the prospect of benefit outweighs the risks for pregnant women and their offspring will depend on a series of factors (see Table A), including characteristics of the vaccine candidate as well as the epidemiological context in which studies are conducted. In some cases, it will be clear that the prospect of benefit far outweighs the risks of receiving the investigational vaccine: for instance, when there is a severe threat in pregnancy, high rate of transmission in the study area, a vaccine candidate that has been developed using a platform generally considered safe in pregnancy, no safety signals from earlier studies, and good indicators of potential efficacy. In other cases, sponsors, investigators, and research ethics committees will have to carefully consider multiple factors to determine whether the risk-benefit profile is favorable for prospective enrollment.

A number of resources have been developed in recent years to provide guidance on protocol design and safety assessments for research on vaccines anticipated to be used in pregnancy, including the guidance developed by the Global Alignment of Immunization safety Assessment in pregnancy (GAIA) and The Brighton Collaboration (see a list of published resources in Appendix C).[120,121,122] Though not restricted to the special case of public health emergencies, these resources specify data that ideally would be acquired prior to enrolling pregnant women in vaccine trials, provide standard definitions for assessment of key obstetric and neonatal health outcomes and of adverse events in pregnancy, and guidelines for protocol development and sequencing of developmental toxicology studies to allow timely enrollment of pregnant women.

Table A: Considerations for Assessing Risks & Benefits of Including Pregnant Women in Vaccine Research & Delivery

Considerations	Specific Dimensions of the Consideration & Expanded Definition	
	Research Context	Deployment Context
1. Likelihood of infection	▶ Likelihood of exposure ▶ Susceptibility to infection – Susceptibility of the pregnant woman – Potential for vertical transmission of pathogen to the offspring	▶ Likelihood of exposure ▶ Susceptibility to infection – Susceptibility of the pregnant woman – Potential for vertical transmission of pathogen to the offspring
	For certain pathogens, pregnant women may be at increased risk of exposure given the routes of transmission combined with social and behavioral norms. For example, pregnant women may be more likely to be exposed to infections that can be transmitted sexually because of decreased condom use in pregnancy. There is also evidence from past SARS and Ebola outbreaks that pregnant women may be more likely to have exposures to certain infections given their increased contact with health care settings for antenatal care.	
2. Probability and severity of harms of infection to pregnant women and offspring	▶ Types of maternal, obstetric, and child harms – Morbidity – Mortality – Pregnancy loss – Pre-term labor – Short- and long-term congenital harms ▶ Probability and severity of these harms often vary based on gestational timing of infection and may vary between pregnant woman and offspring (see below)	▶ Types of maternal, obstetric, and child harms – Morbidity – Mortality – Pregnancy loss – Pre-term labor – Short- and long-term congenital harms ▶ Probability and severity of these harms often vary based on gestational timing of infection and may vary between pregnant woman and offspring (see below)
	Maternal and Obstetric: 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. *Offspring:* 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.	
3. Prospect of immune protection from vaccine	▶ Based on data from clinical trials (phases 1 and 2) – Magnitude and frequency of immune responses – Correlate of protection (if known)	▶ Based on data from clinical trials (phases 2, 3, and 4) – Magnitude and frequency of immune responses – Efficacy against disease endpoints relevant to pregnant women and their offspring – Correlate of protection (if known) – Special considerations relevant to pregnant women and their offspring (e.g., placental transfer of antibody; sterilizing immunity against pathogens that can infect fetus)

(continued)

Table A: Continued

Considerations	Specific Dimensions of the Consideration & Expanded Definition	
	Research Context	Deployment Context
3. Prospect of immune protection from vaccine (cont.)	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.	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.
4. Likelihood and severity of vaccine-associated harms to the pregnant woman or offspring	▶ Safety and reactogenicity – Based on data from prior studies of the specific vaccine candidate – 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)	▶ Safety and reactogenicity – 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 – 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 of protection from 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.	

(continued)

Table A: Continued

Considerations	Specific Dimensions of the Consideration & Expanded Definition	
	Research Context	Deployment Context
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.

Sources: Davey DJ et al., Risk perception and sex behaviour in pregnancy and breastfeeding in high HIV prevalence settings: Programmatic implications for PrEP delivery. PloS one. 2018 May 14;13(5):e0197143; WHO, Addressing sex and gender in epidemic-prone infectious diseases, 2007.

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 and should be expected that some women not known to be pregnant at the time of enrollment will nevertheless be so, or will become pregnant later in the course of the trial. This will occur even when pregnancy tests are required and contraception is advised or provided. Those implementing vaccine trials, whether trials are directed against pathogens that are endemic or epidemic, should develop and include a well-designed, prospective plan to systematically capture data on maternal, fetal, and infant outcomes whenever these unintended exposures occur. These data should be collected using standardized methods and case definitions, such as those proposed by GAIA.[21,22]

Historically, data from inadvertent exposures during pregnancy have been a key source of information regarding the safety profile of vaccines in pregnancy.[123] These data have been used to inform both clinical and public health practice. Of note, data collected from trial participants who are not known to be pregnant at the time of administration can also provide evidence about the effects of vaccine exposure earlier in pregnancy than would be available through trials prospectively enrolling pregnant women. This would include data during the time of organogenesis, which could be important to address safety concerns around teratogenicity.

However, data from inadvertent exposures during pregnancy must be cautiously interpreted, particularly when events occur in early pregnancy. Since up to a third of early pregnancies end in miscarriage, the risk that a "natural" loss will be misattributed to vaccination is a serious concern and should be avoided.[124] Any signals of adverse events, including early pregnancy loss, should be interpreted in the context of the best available data on background rates of pregnancy-specific outcomes (see Recommendations 1 and 3).

Another challenge to interpreting adverse events among pregnant women in the context of vaccine trials conducted in outbreak settings is that the pathogen itself or other agents may be contributing to adverse outcomes, and not the vaccine. Although it may be difficult in an outbreak situation to collect all the needed data, to the extent possible, the study should screen for other possible causes of maternal, fetal, infant, and child harms.

A well-designed plan should also test for relevant correlates of immunity (if known) 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 the pathogen, and to women who may be exposed during pregnancy in future vaccination campaigns.

Box 10: Generating evidence and interrogating safety signals when trial participants become pregnant

A recent informative example includes analyses of the risk of miscarriage among pregnancies conceived within 90 days following administration of an ASO4-adjuvanted bivalent human papillomavirus (HPV) vaccine. In 2010, the Data Safety Monitoring Board for a trial enrolling women and girls of reproductive potential noticed an imbalance in incidence of miscarriage among participants who became pregnant in the HPV arm compared with the control arm—prompting further analysis of the data.[125] The investigators were able to conclude that there was no associated increase in miscarriage or other adverse pregnancy or birth outcomes among women who conceived more than 90 days after vaccination. However, this analysis was unable to "completely rule out the possibility of an increased risk among pregnancies conceived within three months of vaccination."[125] Subsequent analysis of a larger dataset found no evidence of increased risk of miscarriage for pregnancies conceived less than 90 days after vaccination.[126] This example illustrates two key concepts: first, that initial trials may be used for signal detection that can guide future studies; second, that baseline rates or other appropriate comparators of adverse pregnancy outcomes are important, as they were used to assess whether rates of miscarriage among those receiving the HPV vaccine were meaningfully different than rates in their unvaccinated counterparts.

Wherever possible, systematic observational studies that are designed to capture data from inadvertent exposures to vaccine during pregnancy should also include longitudinal evaluation of immunogenicity to assess: the durability of protective immunity for future pregnancies; passive antibody transfer and active immune response among neonates exposed *in utero* (cord blood at minimum); longer-term follow up among children exposed *in utero* to replication-competent candidates to assess for the potential of vaccine-associated congenital harms; and viremia and viral shedding among women exposed to the vaccine. For live vaccines and replication-competent vectors, evaluations of pregnancy-specific safety outcomes and immunity should also include women who become pregnant shortly after administration. These data may help to inform clinical and personal decision-making when pregnancy occurs shortly after immunization.

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

All those implementing vaccine trials that enroll women of childbearing potential, including vaccine trials conducted in outbreak contexts, should have a plan to respond when a participant becomes pregnant.[10,xii] This plan should include asking women who become pregnant whether they would be willing to participate in a long-term follow-up study, as described in Recommendation 12. The plan should also address whether a woman who becomes pregnant before completing a vaccine schedule should be permitted to receive additional doses.

For vaccine trials in which pregnant women are permitted to prospectively enroll, participants who become pregnant after enrollment should be permitted to continue to receive vaccine doses if they choose to do so after a robust re-consent process. The re-consent process should include any pregnancy-specific issues, including those not explicitly or comprehensively addressed in the consent process prior to pregnancy.

In trials in which pregnant women are excluded from prospective enrollment, the determination about continued dosing will be complex, but should not default to presumptive discontinuation. Instead, the decision should be based on an assessment of the best available evidence on the potential benefits and harms of the vaccine for pregnant women and their offspring. The decision should also be based on the particular circumstances of the pregnant participant and the maternal-fetal risks and benefits specific to her situation, including possible risks associated with receiving an incomplete vaccination series and the risks already incurred from the first vaccination (Table A). Here again, 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 completion of the vaccine schedule, women who become aware of a pregnancy while participating in a vaccine trial 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 have already made by volunteering in the original vaccine study.

xii. CIOMS guidance recommends that all trials enrolling women of childbearing potential should inform the women participating of potential risks to the fetus if they become pregnant and guarantee access to effective contraceptive options (Guideline 18). Nevertheless, even in ideal circumstances, many women become pregnant while enrolled in trials. CIOMS guidance also endorses the the position that *"When there is no evidence on the basis of which a potential harm to the fetus can be assumed, women who become pregnant should not automatically be removed from the study, but must be offered the option to continue or end their participation."* We go a step further to state that any evidence of risk from additional vaccine doses would have to outweigh prospect of benefit to deny these women opportunities to complete the vaccine schedule in the study.

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 for which the prospect of benefit outweighs the risks, 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. CIOMS, PAHO, and Subpart B of the U.S. Code of Federal Regulations (45 CFR Part 46) are clear that pregnancy is no exception to the principle that competent adults are the locus of consent for trials that offer the potential to benefit them.[9,10,127] Further, requiring the consent of additional actors can present a material barrier to the benefits research may offer to the offspring—a core rationale in pediatric research for not requiring consent to be procured from both parents when the research offers the child the prospect of direct benefit.

Researchers should support pregnant women who wish to involve partners, family members, and other personal supports in the decision to join or remain in vaccine trials. It is important for community trust that fathers[xiii] and other partners are given the opportunity to engage with and learn about the trial, and there may be cultural contexts in which accommodations should be made to facilitate a woman's ability to engage her spouse or family when she believes it would be helpful or important before agreeing to participate in a research study.[127] That said, at the end of the day, for any research involving the prospect of direct benefit, to either the pregnant woman or her offspring, her consent, and hers alone, should be sufficient.

Oversight entities, such as research ethics committees, should be aware of any added consent requirements that might be mandated by the specific regulations governing proposed protocols. It is worth noting, for instance, that Subpart B of U.S. regulations 45 CFR 46 governing research with human subjects currently requires the father's additional consent for one unusual scenario, namely, research that holds out the prospect of direct benefit solely to the fetus, but offers no prospect of clinical benefit to the woman (with exceptions for the father's unavailability, incompetence, or temporary incapacity, or in cases of pregnancy resulting from rape or incest). This requirement has been strongly criticized as problematic, often unworkable in practice, and out of step with parental consent for pediatric research offering the prospect of direct benefit, which requires only one parent to consent.[128,129] Still, researchers will need to be compliant with governing regulations. Fortunately, Subpart B should only rarely be at issue in vaccine studies conducted in outbreak contexts because the investigational vaccine is very likely to offer pregnant women themselves the prospect of direct medical benefit. Even if the future child is likely to benefit more than the pregnant woman, the fact that the woman

xiii. We use the term "father" in this instance to refer to the male who would be the biological father of any child resulting from the pregnancy. We recognize that the contribution of genetic material resulting in a pregnancy does not alone constitute "fatherhood"—in general and especially prior to the birth of a child. Nor does it imply that the individual involved in conception has an active relationship or partnership with the pregnant woman who would give her consent. We use the term, "father," however, because it is easiest to understand in the context of seeking paternal involvement in any consent processes and because it reflects the langauge included in various regulations governing human subjects research.

stands to benefit on her own ensures that only the pregnant woman's consent is needed under Subpart B.

In some regulatory contexts, there may be explicit requirements that the father's consent be obtained for most or all research involving pregnant women, even when there is a prospect of direct benefit to the woman (see Box 11). Although the pregnant woman's consent should be sufficient to authorize participation, researchers must be aware of the local laws in the setting in which they are conducting a trial and comply with any legal paternal consent requirements. However, they should support the work of gender and health advocates and others to change the requirement.

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.

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 and evaluations affecting them will be made in careful, thoughtful, and evidence-based ways, involving the most informed experts possible. In Recommendation 6, we put forward for consideration that the WHO create a body of interdisciplinary experts to inform decisions about vaccine use in pregnancy in the public health response context. Here we make a similar recommendation to have appropriate expertise informing various activities related to vaccine R&D.[40,xiv] In this instance, experts will need to be integrated into the multiple bodies that deliberate on funding, trial design, research ethics oversight, and data analysis.

Box 11: Examples of Paternal Consent Requirements

In Saudi Arabia, Article 26 of the Implementing Regulations of the Law of Ethics of Research on Living Creatures necessitates that researchers seek informed consent from both the pregnant woman "and her husband," making no exception in cases of benefit to the pregnant woman.[130] Similarly, the Ugandan National Guidelines for Research involving Humans as Research Participants requires that informed consent be obtained from both the mother and father unless "the purpose of the research is primarily to meet the health needs of the mother."[131] In this case, paternal consent is required if the purpose of the research is to benefit both the fetus and the mother, which is likely to be the case for many vaccine studies. Similar paternal consent requirements exist in several Latin American countries.[132]

xiv. This recommendation is consistent with a call from U.S. CDC and HHS officials to establish "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 to inform development, evaluation, implementation, and analysis of trials. See: Faherty LJ, Rasmussen SA, Lurie N. AJOG. 2017.

The involvement of experts in obstetrics and gynecology, maternal-fetal medicine, pediatrics, neonatology, and research ethics in setting priorities for funding will help ensure that pregnant women and their offspring will not be overlooked as vaccine candidates are selected for investment. Similarly, the involvement of these experts 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 risk and prospect for benefit to pregnant women and their offspring of participation and non-participation. Of particular value will be experts in maternal and child health and in research ethics who have a demonstrated commitment to advancing the evidence base in pregnancy and who have experience with infectious diseases, immunology, and maternal immunization.

Including this diversity of relevant expertise will also strengthen the validity and utility of these evidence-generating activities by helping to ensure the identification of appropriate endpoints and the interpretation of findings in terms of 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 developmental changes in offspring, both pre- and post-birth.

Another reason for including maternal health experts in vaccine research and development decisions is that obstetricians/gynecologists, midwives, and other women's health practitioners will be an important group in the deployment of vaccines to pregnant women. Their willingness to endorse and participate in the immunization of pregnant women may be enhanced if experts in their fields have been involved in the development and testing of the vaccine.

RECOMMENDATION 16

Whenever possible, the perspectives of pregnant women should be considered 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.[9,133,134] The need for engagement is even more pronounced during outbreaks and epidemics, a key lesson of the 2014 Ebola experience.[8,23]

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 also be important to various aspects of study design, including 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.[8,135,136,137]

A number of resources provide guidance on how to engage communities in biomedical research studies and the various approaches to participatory-based research.[10,134] For example, one option is to involve pregnant women in

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 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.[123,140] 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).[119,123,141,142,143,144,145] 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.[108,123] 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.[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.[2,3]

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. Numerous groups have proposed criteria for determining how to ethically set priorities among different groups of potential vaccine recipients.[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.[8,10,23]

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

Some vaccines will be offered to pregnant women during outbreaks and epidemics even when little pregnancy-specific data about the safety of the vaccine are available. When this occurs, an important opportunity emerges to narrow the evidence gap between pregnant women and other population groups by implementing prospective observational studies of pregnant women and their offspring who receive the vaccine as part of the outbreak or epidemic response. If such studies are not conducted, decision-makers in future outbreaks and epidemics will face 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 the development of vaccines against other pathogens.

Other vaccines will be recommended for use in pregnancy during outbreaks or epidemics based on more robust evidence about the safety of the specific vaccine product or vaccine platform. However, even in the best of cases, this evidence will be incomplete and likely considerably less than what is available for other population groups. Only relatively small numbers of pregnant women can receive vaccines in clinical trial contexts. In contrast, when pregnant women are included in the population recommended to receive vaccines in outbreak and epidemic contexts, large numbers of pregnant women and their offspring are involved and can be followed, generating much needed additional data.

There are a range of approaches that can be used to generate evidence about the safety and efficacy of vaccines in pregnancy from programmatic use in an outbreak or epidemic. These include adverse event reporting systems, post-marketing surveillance, and pregnancy registries. However, the best approach for gathering the most relevant evidence is to conduct a prospective observational study that has been planned in advance and is properly resourced. If carefully designed, executed, and analyzed, post-authorization studies can provide critical information for the optimal and appropriate use of vaccines in pregnancy.

In some cases, regulatory authorities can request or require that sponsors conduct phase 4 studies. For instance, the U.S. FDA can require sponsors to conduct additional 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.[152] Similarly, the European Medicines Agency has a variety of post-authorization measures that can be requested or required.[151] These include specific obligations that can be imposed for products approved with conditional marketing authorizations, a pathway potentially available in emergency situations.[152] Other national regulatory authorities may also have provisions for requesting or requiring post-market research. Whenever possible, these and other regulatory requirements should be leveraged to support development of an adequate evidence base for vaccines in pregnancy.

Box 13: Resources for Conducting Post-Authorization Observational Studies with Pregnant Women

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" and the Agency plans to release a new population-specific chapter for Pregnant and Breastfeeding Women for public consultation in late 2018.[153] Similarly, the FDA provides general guidance for industry on post-marketing studies and clinical trials—with an updated draft guidance document currently under review.[13,154] An article authored by GlaxoSmithKline employees provides a manufacturer's perspective on how to strengthen post-authorization safety studies (PASS) of vaccines, which included a description of a study prospectively designed to assess the safety of the ASO3-adjuvanted H1N1 influenza vaccine in pregnant women.[155] Other resources specific to generating and harmonizing safety data for vaccines in pregnancy—including in phase 4 studies—are available from the GAIA project and The Brighton Collaboration (see Appendix C). These resources and guidelines should be leveraged in developing post-authorization studies and pharmacovigilance plans for vaccines for outbreak and epidemic contexts to help generate the best possible evidence on the safety and efficacy of these vaccines in pregnancy. The prospective study of killed oral cholera vaccine in Malawi provides an illustrative example of how these post-authorization studies can be conducted, and the advantages that a prospective design offers over retrospective studies.[156,157,158]

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 noted in Recommendation 14 and elsewhere in this Guidance, pregnant women are the moral equals of other self-governing adults. 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 be the proper locus of 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.

There are a few jurisdictions and several cultures that do not accept this premise, and require the authorization of husbands, fathers, or other authority figures instead of or in addition to the consent of the woman for medical interventions.[159] Public health and clinical professionals may be legally

obligated to follow this practice. Even where it is prevailing custom rather than law that imposes the requirement, it may be prudent to follow the practice if that is the best way in an outbreak or epidemic to ensure that pregnant women and their offspring, and women generally, benefit from the protective effects of the vaccine. ***However, public health and clinical professionals should challenge the practice of requiring additional authorizations beyond that of the pregnant woman whenever it is possible to do so without compromising the preferences of pregnant women or the near-term health and safety interests of pregnant women and their offspring.***

Regardless of whether prevailing law and custom respect the decisional authority of pregnant women, public health and clinical professionals should also respect the preferences of pregnant women who wish to engage their partners or other family or friends in decisions about vaccination.

There may be epidemic contexts where the threat is so great and the transmissibility so high that it is ethically justifiable to relax or even suspend consent requirements for vaccine administrations, particularly when the vaccine deployed is licensed or registered. Under these circumstances, pregnant women should be treated no differently from other self-governing adults who are also targets for vaccination.

Jurisdictions differ in the age at which young people are legally permitted to authorize medical interventions, including vaccinations, without parental consent. Some jurisdictions may recognize pregnant young people as sole medical decision-makers at an earlier age than non-pregnant minors. Also, in an epidemic context, jurisdictions may relax parental consent requirements for vaccines and other countermeasures as part of an emergency response.

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 the vaccine 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 groups that cannot receive the vaccine, should be given preferential access to alternative preventive interventions and treatments.

The availability of alternative interventions that can mitigate the harms of the pathogen, particularly those that have established safety profiles in pregnancy, may be a significant factor in the judgment that the vaccine risks to pregnant women and their offspring outweigh the benefits. When this is the case, it is all the more important that pregnant women be among other similarly situated population groups in being prioritized for these alternative interventions.

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.[164,165,166] 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.[167,168,169,170] 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.[169]

APPENDICES

APPENDIX A

MATERNAL IMMUNIZATION, HISTORICAL EXCLUSION OF PREGNANT WOMEN FROM BIOMEDICAL RESEARCH AGENDAS & PRINCIPLES FOR ETHICAL INCLUSION

Any analysis of 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 IMMUNIZATION

Maternal immunization can offer significant benefits in a variety of ways.[171,172] 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).[173,174,175] In both instances, offspring also benefit. Preventing disease in a pregnant woman protects the fetus from the harms of maternal illness, *in utero* exposures, and/or newborn exposures. Other maternal immunizations are being developed primarily to prevent disease in newborns through passive transfer of maternal antibodies—respiratory syncytial virus (RSV) and group B streptococcus (GBS) are examples.[7,19] Still others, such as Zika virus vaccines, occupy a middle ground. Their primary purpose is to protect the fetus, but the target population is not exclusively pregnant women, and the vaccines will offer direct benefits to adults, such as, in this case, 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.[176,177] However, the critical importance of maternal immunization is now increasingly recognized. In recent years, several National Immunization Technical Advisory Groups (NITAGs) and professional organizations in high-income countries have recommended that pregnant women receive inactivated influenza vaccine and tetanus, diphtheria, acellular pertussis (Tdap) vaccines.[140,178,179] 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.[175] Other vaccines have been endorsed for use 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).[173] Still other vaccines, such as maternal vaccines for RSV and GBS are being developed that are specifically intended for pregnant women.[171,180] 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.[173,181]

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 U.S.: data are insufficient to determine teratogenic risk for more than 98% of drugs approved by the U.S. Food and Drug Administration (FDA) since 2000, and 91% of drugs approved since 1980.[182,183] 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.[182,183]

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 and are required by most drug approval agency guidance if pregnant women are to participate in drug development clinical trials.[184] These data also help to identify areas of potential concern or interest that should be pursued in research to further assess safety in pregnancy.[185]

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. Furthermore, the past practice in research oversight policies of categorizing pregnant women as "vulnerable" encouraged the view that the proper ethical stance toward research with pregnant women was exclusion, rather than careful and thoughtful inclusion.[10] 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.[85,186] 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.[85,172,187] 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.[188,189,190]

For all of these reasons, pregnant women have been treated differently and, we have argued, unfairly in the development of new drugs and biologics.[189,191,192] In contrast to other adults, little if any evidence about safety and efficacy of these products 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.[193,194,195,196]

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.[195,196,197,198] 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.[199] Perhaps most critically, relying on passive systems can lead to long delays in safety determination. In the U.S., 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.[182]

An increasing number of organizations, including WHO, PAHO, CIOMS, ACOG, and the NIH Office of Research on Women's Health now recognize the importance, both scientifically and ethically, of involving pregnant women in research.[8,9,10,11,200,201] They call for a shift to integrating pregnant women into the research agenda, 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.

98% of drugs approved by the FDA since 2000 had uncategorized risks in pregnancy. The mean time to assign a pregnancy-specific risk level for these drugs is 27 years post-approval.

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 equitable 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."[10] CIOMS explicitly includes pregnant women as such a group.

Just allocation of research investments to the health needs of pregnant women is also in accordance with a core commitment of public health ethics to prioritize the needs of disadvantaged groups and to diminish health disparities.[202,203,204] Illness in pregnancy often brings increased risk of disease related-harms for both the pregnant women and any resulting children, especially among the global poor.[205,206,207]

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 U.S. 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.[11,208] It was increasingly realized that such a designation was problematic, tacitly suggesting that pregnant women are incapable of offering valid consent.[128,209,129] 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," 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," anticipated to go into effect January 21, 2019.[10,127]

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.[10,13] 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 A).

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.[10,127] 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" and the Department of Health and Human Services (HHS) regulations carry a provision of increased risk under special HHS Secretarial review.[10,127] While research involving

Box A: 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.

no prospect of direct benefit to woman or future child can be important, it is not generally at issue in vaccine research involving pregnant women.

For trials offering the prospect of direct benefit to the pregnant woman, offspring, 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.[210] The risk is justified by the potential benefits to the subjects. More specifically, the likelihood and importance of the potential benefits must be reasonably judged to outweigh the risks (see Box B). 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.[10]

There is no settled view about whether the prospect of benefit to the pregnant woman alone 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 not to the fetus. These

Box B: 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.

questions are generally less likely to arise in vaccine research around emerging pathogens, because both the pregnant woman and her offspring are likely to benefit from maternal vaccination in these contexts. In these kinds of cases, there is clear agreement that research that has a favorable potential risk-benefit balance to the fetus can proceed so long as other protective regulatory standards are met.

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

The distinction between research studies 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.[192,211,212] 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 to generate valid conclusions on the use of a product in pregnancy, they 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.[10,192,211,212] 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 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.

APPENDIX B

PREVENT APPROACH TO GUIDANCE DEVELOPMENT

The Guidance was co-authored by the 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. Working Group members convened for one in-person meeting over two days in February 2018 and participated in multiple phone and video-conference discussions and email exchanges to develop and refine the Guidance between July 2017 and August 2018.

Beyond the members of our Working Group, we relied on a broad consultation strategy to ensure that the content of our recommendations was informed by wide-ranging areas of expertise and the most-up-to-date information on evolving changes to the epidemic vaccine development and deployment landscape.

The consultation strategy built upon previous engagement efforts conducted between April 2016–June 2017 in support of developing ethics guidance specific to Zika virus vaccines, "Pregnant Women & the Zika Virus Vaccine Research Agenda: Ethics Guidance on Priorities, Inclusion, and Evidence Generation." For the development of the initial ZIKV Guidance, we conducted consultations with more than 60 experts in bioethics, public health, vaccine science and policy, obstetrics, maternal-fetal medicine, pediatrics, pharmaceutical development, and regulatory affairs. A 15-person expert Working Group co-authored the ZIKV Guidance, with many members continuing on to serve on the PREVENT Working Group.

Since publishing the ZIKV Guidance, we have engaged with more than 40 additional experts, including those working in preclinical and clinical vaccine development; regulatory affairs; vaccine policy—particularly as it pertains to vaccine delivery as part of epidemic response; infectious disease epidemiology; maternal, newborn, and child health; and bioethics. These experts come from a wide range of institutions, including but not limited to public health agencies and organizations at national, regional, and global levels; academic institutions; non-governmental organizations that conduct vaccine research and engage in vaccine implementation efforts; global health funding organizations; and multilateral donors. Many of those with whom we consulted had prior experience working in the pharmaceutical industry (both in "big pharma" and in biotechnology companies).

Beyond targeted consultations with these diverse experts, we shared various pieces and draft versions of the guidance document at a number of presentations and roundtable sessions throughout various stages of development. Meetings at which we presented draft guidance materials include:

- Ethox Centre Ethical Design of Vaccine Trials in Emerging Infections Workshop (2017)
- Infectious Diseases Society for Obstetrics and Gynecology (IDSOG) 2017 & 2018 Annual Meetings
- American Society for Bioethics and Humanities 2017 Annual Conference

- The 2nd meeting of the U.S. HHS Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)
- American Society of Tropical Medicine & Hygiene (ASTMH) 2017 Annual Meeting
- A half-day ASTMH satellite workshop hosted at Johns Hopkins Berman Institute
- WHO Product Development for Vaccines Advisory Committee (PDVAC) Consultation on Nucleic Acid Vaccines (February, 2018)
- Interactive Roundtable at the 2018 World Vaccine Congress
- 2018 Annual Conference on Vaccinology Research

We are grateful to all who shared their time and feedback with the Working Group in support of this Guidance.

APPENDIX C
SELECT GAIA RESOURCES

The Global Alignment of Immunization safety Assessment in pregnancy (GAIA) project was formed in response to a call from the World Health Organization for a globally concerted approach to actively monitor the safety of vaccines in pregnancy. GAIA aims to improve the quality of outcome data from clinical vaccine trials in pregnant women, with a specific focus on low- and middle-income countries (LMICs), where the incidence of infectious diseases is highest. The project—coordinated by the Brighton Collaboration Foundation with core funding from the Bill & Melinda Gates Foundation—seeks to improve data generated on immunization in pregnancy by harmonizing maternal, pregnancy, fetal, and neonatal health outcome assessment. GAIA has published a number of resources to this end, including in two special issues of the journal *Vaccine*. These and other select publications are listed below for reference. Additional resources can be found on their website: http://gaia-consortium.net/outputs.

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