Vaccine 62 (2025) 127513

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

A template tool for the evaluation of vaccines for emerging pathogens to be used for pregnant and breast-feeding women

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ARTICLE INFO

Keywords:
Maternal vaccination
Vaccines
Safety surveillance

ABSTRACT

Vaccination during pregnancy provides effective protection against pathogens that increase the risk of maternal and infant morbidity and mortality for mothers and their infants. The SARS-CoV-2 pandemic demonstrated the need for the inclusion of pregnant and breast-feeding women in research and development of vaccines for emerging pathogens, such as Ebola, Zika, Lassa fever, Chikungunya, and influenza virus of pandemic potential.

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https://doi.org/10.1016/j.vaccine.2025.127513
Received 30 August 2024; Received in revised form 3 July 2025; Accepted 11 July 2025
Available online 18 July 2025

Benefit-risk
Template
Pandemic
Emerging pathogens

The COVID-19 Vaccines Global Access (COVAX) Maternal Immunization Working Group (MIWG), in collaboration with the Coalition for Epidemic Preparedness Innovation and the Safety Platform for Emergency Vaccines (CEPI-SPEAC) developed a standardized template with key considerations to guide the assessment of vaccines against emerging pathogens in pregnant and breast-feeding women. The aim of this tool is to enable key stakeholders to perform an early structured assessment of the overall potential benefit and risk for maternal immunization against an emerging pathogen. It can also be used to support risk management and pharmacovigilance planning, communication strategies, policy development, and acceptance of vaccination during pregnancy in future pandemics.

1. Introduction

Globally, an estimated 213 million pregnancies occur annually [1]. Women represent 71 % of the global workforce of the health sector and this percentage is likely to be higher in low- and middle-income countries (LMICs) [2–4]. It is estimated that at any given time in the United States (US) there are over 300,000 women of child-bearing age, i.e., 15–49 years old in the healthcare workforce, and in the WHO regions, 67 % of the healthcare workforce are female, particularly in the nursing and midwifery workforce [5,6]. Healthcare-related occupations are critical during an epidemic or pandemic responses and should, therefore, be prioritized for vaccine allocation, as was seen during the COVID-19 pandemic [7]. In addition, women often have jobs that are associated with high risk of exposure, such as childcare providers, teachers, public-facing and hospitality workers, and caregivers. The COVID-19 pandemic highlighted the urgent need for guidance on immunization strategies for pregnant and breast-feeding women, especially for those who rely on employment in these high-risk occupations.

In addition, pregnant women and their fetuses are at increased risk for severe disease and death from SARS-CoV-2 and other respiratory and emerging pathogens, often in association with pregnancy physiology [8–12]. Older pregnant women (36–44 years), and those who have underlying medical conditions, such as obesity, gestational diabetes or hypertension, might be at higher risk of severe disease, similar to the higher risks seen in older individuals and those with underlying medical conditions in the general population [13–16]. Data from high income countries (HICs) suggest that adverse birth outcomes, such as preterm delivery and stillbirth, are more common among pregnant women infected with SARS-CoV-2, while in endemic areas, pregnant women infected with Ebola and Lassa fever also have higher risk of these outcomes compared with non-infected individuals [13,16–20].

Healthcare access disparities affect pregnant women worldwide. Studies from the US and the United Kingdom reported that Black and Hispanic pregnant women were at higher risk of severe disease and hospitalization than nonpregnant women [12,18]. Limited pregnancy-specific data are available from LMICs, mainly due to a lack of data collection infrastructures. The results from a meta-analysis showed that the overall risk of adverse pregnancy outcomes was higher in LMICs than in HICs (OR 2.4) [21]. COVID-19-related abortion (OR 6.2), stillbirths (OR 2.0), and maternal death (OR 7.8) were more common in LMICs compared with HIC [21]. Additional data will be needed to inform local decision-making and improve acceptance of vaccines for pregnant and breast-feeding women.

2. Vaccines against emerging pathogen for pregnant women

Vaccines for pregnant women are one of the most important public health measures undertaken globally to reduce the burden of disease in mothers and infants from tetanus, pertussis and seasonal influenza. During previous pandemics caused by respiratory pathogens, such as influenza A/H1N1pdm09, infection in pregnant women was associated with an increased risk for severe disease and hospitalization, and pregnant women have subsequently been prioritized for immunization [22–24]. Ebola vaccines are being evaluated in pregnant women in epidemic regions in West Africa, with observational studies evaluating vaccines since 2016 and interventional studies since 2020 [25,26].

Various organizations, including the U.S. National Academy of Medicine (NAM), the American College of Obstetrics and Gynecology (ACOG), the Pregnancy Research Ethics for Vaccines, Epidemics, and new Technologies (PREVENT) group, and the World Health Organization (WHO), supported the position that pregnant and breast-feeding women are a priority population that must not be excluded from COVID-19 vaccine allocation strategies [23,27–30]. Reports from observational cohort studies conducted in countries that included pregnant women early in their COVID-19 vaccine implementation strategies, such as Israel, demonstrated a significantly lower risk of SARS-CoV-2 infection among vaccinated pregnant women compared with unvaccinated pregnant women (adjusted hazard ratio 0.22, 95 % CI: 0.11–0.43) [31].

The Council for International Organizations of Medical Sciences (CIOMS) and the United Nations AIDS/World Health Organization guidelines, in 2002 and 2005, respectively, encouraged the inclusion of pregnant women in clinical studies [32,33]. More recently, the U.S. Food and Drug Administration (FDA) draft guidance for the pharmaceutical industry also supported for the inclusion of pregnant women in clinical trials [34]. Exclusion of pregnant women from clinical trials can lead to a lack of data that is needed to make informed decisions about the potential benefits and risks of medications and vaccines administered during pregnancy.

It has been reported that recruitment and retention of pregnant women in clinical trials is challenging [35–37]. Although pregnant women have been reported to be willing to participate in clinical research, they are more willing to participate in observational or retrospective studies or life-style interventional studies than randomized trials, particularly those including placebo groups [38,39]. Strategies for encouraging pregnant women to participate in clinical trials should be evaluated [39].

In 2020 in their guidance for developing and licensing COVID-19 vaccines FDA encouraged vaccine manufacturers to collect and consider "*data that might support inclusion of pregnant women and women of childbearing potential who are not actively avoiding pregnancy in pre-licensure clinical trials*" because the use of "*COVID-19 preventive vaccines during pregnancy and in women of childbearing potential will be an important consideration for vaccination programs*" [40]. However, the guidance did not specify what data should be collected.

3. The COVAX-CEPI-SPEAC maternal immunization working group

In April 2020, in response to the COVID-19 pandemic, a global collaboration, the Access to COVID-19 Tools (ACT) Accelerator, was launched to facilitate the development, production of COVID-19 tests, treatments, and vaccines, and to ensure equitable access [41]. The ACT Accelerator's SARS-CoV-2 vaccine research, development and manufacturing workstream included a Clinical Development and Operations Specialized Working Team (SWAT) to identify tools and provide support for vaccine developers to facilitate COVID-19 vaccine licensure. The SWAT team established the COVID-19 Vaccines Global Access and Coalition of Epidemic Preparedness Innovation (COVAX-CEPI) Maternal Immunization Working Group (MIWG) in August 2020 to address the

needs of pregnant and breast-feeding women during the COVID-19 pandemic. In 2022 the group integrated into the Special Populations MIWG of the Safety Platform for Emergency Vaccines (SPEAC)-Brighton Collaboration project supported by CEPI. The members of the MIWG included professionals with expertise in various aspects of maternal immunization that represented diverse backgrounds, organizations, and geographical settings (Appendix 1).

The principal goal of the MIWG is to facilitate access to vaccine candidates that are suitable for use in pregnant and breast-feeding women by:

1) identifying approaches for the evaluation of vaccine candidates from pre-licensure clinical trials to the post-licensure period, using COVID-19 vaccines as a model;
2) creating an evaluation framework for vaccine candidates for use in this population; and
3) identifying the data and studies that are needed to close the gap in the availability and access to safe and effective vaccination and prevention strategies for these women.

Three work stream groups were set up to cover issues relevant to the inclusion of pregnant women in the vaccine development pathway, from the pre-clinical phase through to the post-licensure phase. During weekly or bi-weekly meetings, work stream representatives shared their findings with the group and identified areas of consensus to refine and address their key questions. The groups also solicited input from external subject matter experts as needed. Ethics and regulatory advisors in the group reviewed work stream discussions and outputs and provided guidance.

4. Description of proposed evaluation framework for vaccine development for use in pregnant and breast-feeding women

The MIWG developed key questions to be used as an evaluation framework for all stages of vaccine development for different vaccine platforms for use in pregnant and breast-feeding women, including in future pandemics or outbreaks (Table 1). The framework was designed to guide the evaluation of candidate vaccines rather to be used as a mandatory checklist. It is not intended to be either exhaustive or required in all instances and should not hinder the development of clinical trial protocols.

The key questions table is divided into sections addressing general topics for the evaluation of candidate vaccines in pregnant and breast-feeding women (Table 1). The questions were developed to be used as a guide for the assessment of vaccines. It is recommended to start with the questions in Section A and work through the sections sequentially to Section E. These questions serve as a guide and it is possible that not all questions will be completely answered, and, in some situations, some may not even be addressed if data is not available (e.g. in LMIC). The sources of information, as well as the date of the data review should be documented for each answer. These sources may include publications, studies in progress, guidance documents, policy statements, vaccine recommendations, and others, as pertinent. The key questions may be readdressed, as new information emerges.

The questions in section A establish the impact and burden of the disease or pathogen in this population, as well as in the infants' fetal and neonatal periods. Those is section B aims to seek product or platform specific information. Some of this information will not be unique to this population, but any data from adult populations, particularly women of childbearing age, will be informative. It is recommended to use the BRAVATO (Brighton Collaboration Benefit-Risk Assessment of Vaccines by Technology) templates for specific vaccine constructs to gather product-specific information, and to complete these with additional pregnancy-related questions provided in the questionnaire [42].

The questions in section C aim to collect information relevant to all vaccines that can be considered for pregnant and breast-feeding women, irrespective of the specific product or vaccine platform. Some of the questions may need to be fully addressed before vaccine studies or implementation are possible. It is recommended to seek relevant regulatory agency guidance to determine which items need to be addressed at each phase of vaccine development.

The questions in section D seek information for the safety evaluation of all vaccines to be used in pregnant and breast-feeding women, both during clinical trials as well as post-licensure. It is recommended to consider the establishment of safety surveillance plans, registries, retrospective studies and evaluation, etc. These activities should include clear communications and risk mitigation plans, educational activities, and promotion of vaccination.

Lastly, the questions in section E provide a suggested framework to summarize the results of the evaluation and assessment of candidate vaccines used in pregnant and breast-feeding women, identify data gaps, and serve as a tool for generating hypotheses for further research and surveillance, as well as for developing vaccine implementation plans.

5. Conclusion

It is essential to include pregnant and breast-feeding women in studies assessing vaccines against emerging pathogens, as they are often at high-risk for severe disease and potential adverse maternal and neonatal outcomes. Their inclusion in studies is critical to generate robust pre-licensure data on vaccines. Data for pregnant and breast-feeding women should continue to be assessed in post-licensure surveillance and other evaluations, to help identify which candidate vaccines and which approved vaccines are safe and optimal for use in these special populations. Concerted efforts are needed to alleviate concerns that vaccines for emerging pathogens will be rushed to market without adequate safety evaluation in pregnant and breast-feeding women.

The key questions developed by the MIWG will be a valuable tool for researchers and other key stakeholders to assess the suitability of new vaccines for pregnant and breast-feeding women. When feasible, pregnant and breast-feeding women should be included in vaccine trials to help guide regulatory and policy recommendations at the time of licensure or shortly after. Post-approval (e.g., under emergency or compassionate use authorization) or continued post-licensure surveillance studies will be necessary to characterize the benefit-risk profile in larger populations of pregnant and breastfeeding women.

The purpose of this tool is to provide a template for researchers and decision makers to consider the relevant aspects necessary to support the use of a vaccine in pregnancy or post-partum, with all elements considered important, and therefore not prioritized or mandated. The use of this tool should not hinder the development of clinical trials in emergency situations, including in LMIC, where the availability of some data might be limited. Input from pertinent regulatory agencies should be sought throughout the process of evaluation and implementation of vaccines for pregnant and breast-feeding women.

Author contribution

All authors participated in the Maternal Immunization Working Groups, reviewed the drafts and validated the final manuscript for submission.

ICMJE criteria

All authors attest they meet the ICMJE criteria for authorship.

CRediT authorship contribution statement

Flor M. Munoz: Writing – review & editing, Writing – original draft, Funding acquisition. **Beate Kampmann:** Writing – review & editing, Writing – original draft. **Andy Stergachis:** Writing – review & editing, Writing – original draft. **Manu Chaudhary:** Writing – review & editing,

Table 1
Key questions for the evaluation of candidate vaccines for emergent pathogen for pregnant and breast-feeding women: What is the evidence that pregnant and breast-feeding women need to be immunized against this pathogen?.

Section A. Key questions about the pathogen, disease, and pregnancy
A1 What is known about the risk in pregnant and non-pregnant women of child-bearing age
A1.1 Are pregnant women at greater risk of infection-related complications than non-pregnant women of child-bearing age?
A1.2 What are the clinical manifestations of disease in pregnant women?
A1.3 Are the clinical manifestations similar to those in non-pregnant women of child-bearing age?
A1.4 Are pregnant women at greater risk of severe disease (e.g. intensive care admission, death) than non-pregnant women and the general population?
A1.5 Is the hospitalization rate higher in pregnant women compared with non-pregnant women and the general population?*
A1.6 Is the intensive care admission rate higher in pregnant women compared with non-pregnant women and the general population?**
A1.7 Is the risk of death higher in pregnant women than in non-pregnant women of child-bearing age and the general population of the same age?
A1.8 Are there any disease effects or complications that are specific to pregnant women?
A1.9 Is the risk of infection higher during a specific gestational trimester?
A1.10 Is the risk of severe disease higher during a specific gestational trimester?
A1.11 Is the risk of maternal death higher during a specific gestational trimester?
A1.12 Are there known maternal factors or underlying medical conditions that increase the risk of infection, severe disease, or death?
A1.13 What factors or underlying medical conditions increase the risk of infection, severe disease, or death during pregnancy?
A2. What is known about treatment for pregnant women?
A2.1 Have pregnant women been included in clinical trials of treatments and vaccines for this disease?
A2.2 What are other potential effects of infection and disease in pregnancy?
A2.3 Are there specific, safe and effective treatments available for pregnant women?
A2.4 What is the efficacy of existing treatments in pregnant women?
A3. What is known about the effect of the pathogen on pregnancy and obstetric outcomes
A3.1 What are the adverse obstetric outcomes associated with maternal infection and disease?
A3.2 What is the risk of preterm labor in infected women compared with non-infected women?
A3.3 What is the risk of preterm delivery in infected women compared with non-infected women?
A3.4 What is the rate of caesarean deliveries in infected women compared with non-infected women?
A3.5 What are the indications for caesarean delivery in infected women?
A3.6 What are the risks for specific maternal obstetric complications associated with infection and disease during pregnancy, including:
A3.6.1 Hypertension disorders, eclampsia, preeclampsia?
A3.6.2 Gestational diabetes?
A3.6.3 Antenatal and perinatal bleeding?
A3.6.4 Chorioamnionitis?
A3.6.5 Maternal infection and sepsis?
A3.6.6 Post-abortion and postpartum endometritis?
A4. Is there any evidence for vertical transmission of the pathogen and natural immunity?
A4.1 Describe any evidence for vertical transmission via the placenta?
A4.2 Describe any evidence for vertical transmission via breastmilk?
A4.3 Is there evidence of placental infection?
A4.3.1 If yes, what are the mechanisms of placental infection?
A4.4 Is there evidence of transplacental transfer of immunity after natural infection?
A4.4.1 If yes, during which trimester is the highest level of antibody transfer?
A4.5 Is there evidence of transfer of immunity via breast milk after natural infection?
A5. Effects of maternal infection on the fetus
A5.1 Does fetal infection occur?
A5.2 What is the risk of fetal infection?
A5.2.1 What is the risk of fetal infection by trimester of gestation?
A5.2.2 Is there evidence of teratogenicity or congenital malformations from infection?
A5.3 What is the risk of teratogenicity?
A5.4 Is there a risk of fetal loss?
A5.5.1 Does the risk of fetal loss vary by gestational trimester?
A5.6.2 What is the risk of spontaneous abortion or miscarriage?
A5.7.3 What is the risk of stillbirth?
A5.8 What is the risk of intrauterine growth restriction?
A5.9 Are there other fetal effects or risks associated with maternal infection with the pathogen?
A6 Effects of maternal infection on neonates and infants
A6.1 What is the risk of prematurity following maternal infection?
A6.2 What is the risk of neonatal infection?
A6.3 What is the mechanism of transmission of neonatal infection from mother to infant?
A6.4 What are the clinical manifestations of neonatal infection?
A6.5 What is the risk of severe neonatal disease?
A6.6 What is the risk of neonatal death?
A6.7 What are the risks of neonatal sepsis, meningitis and other infections?
A6.8 What are the risks of infection, disease and death in the first six months of life?
A6.9 What are the risks of infection, disease and death in the first year of life?
A7 Post-partum and breast-feeding women:
A7.1 Are post-partum and breast-feeding women at greater risk of infection?
A7.2 What are the infection rates in post-partum and breast-feeding women compared with non-pregnant women and non-breast-feeding post-partum women?
A7.3 Are post-partum and breast-feeding women at greater risk of severe disease compared with non-pregnant women and non-breast-feeding post-partum women?
A7.4 Is the hospitalization rate higher in post-partum and breast-feeding women compared with non-pregnant women and non-breast-feeding women?
A7.5 Is the rate of intensive care admission greater in post-partum and breast-feeding women with infection compared to non-pregnant and non-breast-feeding post-partum women?
A7.6 Is the risk of maternal death during post-partum period greater than in the non-pregnant population?
A7.7 Is the risk of maternal death greater in breast-feeding women than non-breast-feeding women?
A7.8 Are there complications specific to port-partum and breast-feeding women?
A7.9 Are there available antiviral or other specific therapies for post-partum and breast-feeding women?
A7.10 What is the efficacy of available treatments in post-partum and breast-feeding women?
A7.11 Are post-partum and breast-feeding women included in clinical trials of treatments and vaccines?

Section B. Key questions about specific vaccine platforms and components

B1 What safety data are available to show that use of the vaccine in pregnancy and breast-feeding is safe?
B2 Vaccine name and manufacturer
B3 Vaccine construct or platform (use BRAVATO tables in Appendix II for specific non-pregnancy questions)
Protein or subunit (Appendix II.A) [43]
Nucleic acid (Appendix II·B) [44]
Viral vector (Appendix II·C) [45]
Live attenuated vaccines (Appendix II·D) [46]
Inactivated vaccines (Appendix II.E) [47]
B4 General and pre-clinical toxicology studies on vaccine construct and components
B4.1 Are there any safety data from pregnant and non-pregnant animal models for the vaccine construct or platform or any of the vaccine components?
B4.2. Have developmental and reproductive toxicity studies (DART) been conducted?
B4.2.1 If, yes, describe these studies and indicate which components of the vaccine were evaluated (complete vaccine construct or specific components)
B4.2.2 If yes, describe any developmental or reproductive toxicities identified?
B4.2.3 Were any other pregnancy-related issues associated with any of the specific components of this vaccine identified in animal studies?
B4.2.4 If yes, describe these issues
B4.3 Are there any placental biology data for this vaccine construct or platform or any of the components? If yes, describe
B5 Vaccine construct- or platform-specific questions
B5.1 Are there any pregnancy-related issues in clinical studies associated with the vaccine specific construct or platform or any of the components? If yes, describe
B6 Antigen, adjuvant and other components-specific questions
B6.1 Were pregnancy-related issues associated with the antigen, adjuvant or other specific components of this vaccine in clinical studies? If yes, describe.
B7 Construct or platform-specific data in humans: non-pregnant population
B7.1 Are there any safety data for licensed vaccines that use this specific construct or platform in non-pregnant populations? If yes, describe
B7.2 Are there any safety data from clinical trials using this specific construct or platform in non-pregnant populations, even if not licensed? B7.2.1 If yes, describe
B8 Construct or platform-specific efficacy and effectiveness data in humans: non-pregnant population
B8.1 Describe the mechanism or correlates of protection
B8.2 Are there any efficacy data from clinical trials using this specific construct or platform in non-pregnant populations? If yes, describe
B8.3 Are there any efficacy or effectiveness data for licensed vaccines that use this specific construct or platform in non-pregnant populations? B8.3.1 If yes, describe
B9 Construct or platform-specific safety data in humans: pregnant populations
B9.1 Are there any safety data for pregnant women in early clinical studies using this specific construct or platform, even if not licensed?
B9.2 Are there any safety data for pregnant women who were inadvertently exposed, during clinical trials or not?
B9.3 Are there any safety data for breast-feeding women?
B9.4 Are there any pregnancy-related safety issues associated with this specific construct or platform?
B10 Construct or platform-specific efficacy/effectiveness data in humans: pregnant population
B10.1 Describe the mechanisms or correlates of protection
B10.2 Are there any efficacy or effectiveness data from early clinical trials or pharmacokinetic or pharmacodynamic studies using this specific construct or platform, even if not licensed?
B10.2 Are there any efficacy data for pregnant women exposed inadvertently or intentionally or real-world effectiveness data for pregnant women receiving the vaccine post-licensure?
B10.3 Are there any efficacy or effectiveness data for breast-feeding women?
B10.4 Are there any pregnancy-specific efficacy issues associated with this specific construct or platform? If yes, describe.
B11 Other vaccine components: pregnancy-specific questions
11.1 What is known about the delivery system (e.g., lipid nanoparticles) or other components of the vaccine in pregnancy?
11.2 What is known about transplacental transfer of these delivery systems and components?
11.3 What is known about the permanence of vaccine delivery or other components in tissues?
B12 Vaccine storage, delivery and administration characteristics
B12.1 Is vaccine use in the context **of antenatal care** feasible?
B12.1.1 Describe vaccine storage requirements in relation to antenatal care needs/settings
B12.1.2 Describe vaccine administration requirements
B12.1.3 Describe the number of doses needed and interval between doses
B12.1.4 Describe specific considerations for vaccine administration in relation to other vaccines that are given during pregnancy (e.g., influenza, tetanus, pertussis).
B12.1.5 Describe specific considerations for vaccine administration in relation to medications or other vaccines that are or could be given during pregnancy.

Section C. Key questions about the development and planning for all candidate vaccines (regardless of construct or platform) for pregnant and breast-feeding women and their exposed offspring

C1 Pre-clinical pregnancy data
C1.1 Are results of DART studies available or required?
C1.1.1 DART study completion dates or expected completion date
C1.1.2 Findings of DART studies (also see questions in Section B.3)
C2 Clinical development status and plans for the vaccine in non-pregnant populations
C2.1 Target populations in clinical studies
C2.1.1 Planned studies: planned total enrolment (answer for each: phase 1, phase 2, phase 3)
C2.1.2 Ongoing studies: planned total enrolment (answer for each: phase 1, phase 2, phase 3)
C2.1.3 Completed studies: total enrolment (answer for each: phase 1, phase 2, phase 3)
C2.2 Location of clinical studies
C2.2.1 Where are(were) the clinical studies conducted? List all countries
C2.2.2 Will studies be conducted in high-income countries (HICs) and low- to middle-income countries (LMICs) countries simultaneously?
C2.2.3 Will the approved vaccine be distributed in HICs and LMICs countries simultaneously?
C2.2.4 Will vaccine be distributed in epidemic or endemic areas?
C3 Safety data for non-pregnant populations
C3.1 Vaccine reactogenicity (after each dose)
C3.1.1 Proportion of individuals with fever, frequency and duration of fever after each immunization, need for pre-emptive or symptomatic treatment
C3.2 Adverse events following immunization (AEFIs)
C3.3 Serious adverse events (SAEs)

(*continued on next page*)

Table 1 (*continued*)

C3.4 Adverse events of special interest (AESIs)
C3.5 Duration of safety follow up
C4 Immunogenicity data from non-pregnant populations
C4.1 Is there an accepted correlate of protection? (include assessment of data quality)
C4.2 Antibody responses (include assessment of data quality)
C4.3 Cell-mediated immunity (CMI) (Th1 vs. Th2) responses (include assessment of data quality)
C4.4 Duration of immunity (include assessment of data quality)
C4.4.1 How is immunity defined? (antibodies? CMI? other?)
C4.4.2 What is the duration of follow up and protection?
C4.5 Is there a need for repeated immunizations?
C5 What efficacy data are available for non-pregnant population?
C5.1 What are the efficacy outcomes? (e.g., protection against infection? symptomatic infection? severe disease? death?
C5.2 Efficacy after partial vaccination?
C5.3 Efficacy after complete vaccination?
C6 Inadvertent exposure during pregnancy in clinical studies in non-pregnant populations
C6.1 Is there a plan to capture data for women who become pregnant during clinical trials? Describe plan or protocol, as well as the mechanism for reporting outcomes
C6.2 Will women who become pregnant during the clinical trial have the option to remain in the trial? Yes/no: explain rationale and plan
C6.3 What immunogenicity data are being/will be collected from women who become pregnant during the clinical trial?

6.3.1 Describe immunogenicity data, if any, collected to date
C6.4 What safety data are being/will be collected from women who become pregnant during the clinical trial?
C6.4.1 Describe any safety data collected to date. Include data collection forms and mechanism for reporting outcomes
C6.5 What efficacy data are being/will be collected from women who become pregnant during the clinical studies?
C6.5.1 Describe any efficacy data collected to date.
C6.6 What is the duration of follow-up for women who become pregnant in clinical trials? (include length and intervals of follow-up)

6.6.1 Describe follow-up data, if any, collected to date
C6.7 What is the plan for collection of data from women in post-partum period?

6.7.1 Describe post-partum data, if any, collected to date.
C6.8 What is the plan for follow up and collection of safety and efficacy data in the infants born after women became pregnant in clinical trials?
C6.8.1 Describe any infant data collected to date
C7 Communication plan for inadvertent exposures in pregnant women
C7.1 What is the plan for analyzing and sharing data about inadvertent pregnancy exposure to vaccine during clinical trials?
C8 Inclusion of pregnant women in clinical trials
C8.1 Is there a plan to enroll pregnant women in clinical studies?
C8.1.1 If no, what is the justification for exclusion?
C8.2 What is the plan for recruitment of pregnant women into clinical studies? Describe
C8.3 What immunogenicity data are being/will be collected from pregnant women in clinical studies?
C8.3.1 Describe any immunogenicity data collected to date
C8.4 What safety data are being or will be collected from pregnant women in clinical studies?
C8.4.1 Describe any safety data collected to date
C8.5 What efficacy data are being/will be collected from pregnant women in clinical studies?
C8.5.1 Describe any efficacy data collected to date.
C8.6 Is there a plan to collect data from women in the post-partum period?
C8.6.1 If yes, describe
C8.6.2 If no, explain the justification
C8.7 Is there a plan for the collection and testing of breastmilk from post-partum women who were enrolled in clinical studies while pregnant?
C8.7.1 If yes, describe
C8.7.2 If no, what is the justification
C8.8 Is there a plan for the collection and follow up of infants of women enrolled in clinical studies while pregnant?
C8.8.1 If yes, describe the protocol, safety, immunogenicity, efficacy data being collected, as well as duration of follow up
C9 Communication plan for pregnancy exposures in clinical studies
C9.1 What is the plan for analyzing and sharing information about vaccine administration to pregnant women enrolled in clinical trials?
C10 Plan for inclusion of breast-feeding women in clinical trials
C10.1 Is there a plan to include breast-feeding women in clinical trials?
C10.1.1 If yes, describe the plan
C10.1.2 If no, what is the justification for their exclusion?
C10.2 Is there a plan for the collection and testing of breastmilk from breast-feeding women enrolled in clinical studies? (also see questions in Section C.16)
C11 Fetuses, neonates and infants
C11.1 What is the plan for collection of data from fetuses of exposed pregnant women enrolled in clinical studies?
C11.2 What is the plan for capture of data from neonates whose mothers were exposed in clinical studies?
C11.3 What is the plan for follow-up of infants whose mothers were exposed in clinical studies? Describe, including intervals and duration
C11.4 Will infant antibody titers be measured following birth to assess levels and duration after exposure? (also see questions in Section C17)
C12 Vaccine approval for pregnant women
C12.1 What additional data is needed for vaccine approval for pregnant women?
C13 Pregnancy-specific safety questions
C13.1 What reactogenicity is acceptable in pregnancy?
C13.1.1 Percentages of individuals with fever, severity of fever, duration of fever
C13.1.2 Local reactogenicity
C13.1.3 Systemic reactogenicity
C13.1.4 Other
C14 Timing of vaccination during pregnancy
C14.1 What should be the preferred timing of vaccination during pregnancy and why?
C14.2 Is the dosing schedule amenable to administration during pregnancy?
C14.3 Can the full dose series be completed during pregnancy?
C14.4 Can the dose series include pre- or post-pregnancy administration?

(*continued on next page*)

Table 1 (*continued*)

C14.5 Can the dose series be administered with other vaccines given during pregnancy?
C14.5.1 If, yes, what are the considerations for concomitant vaccination?
C15. Adverse events in pregnant women
C15.1 What adverse events following immunization (AEFIs) should be monitored?
C15.1.1 Maternal
C15.1.2 Obstetric
C15.1.3 Fetal, neonatal
C15.2 What outcomes of special interest (AESIs) should be monitored?
C15.3 What is the risk of vaccine-associated enhanced disease (VAED)?
C15.4 What is the risk of breakthrough infection and post-infection complications?
C15.5 What is the risk for obstetric complications?
C15.6 What is the risk for neonatal complications?
C15.6.1 Are AEs in infant associated with gestational age and timing of exposure?
C16. Breast-feeding-specific questions
C16.1 Is there a plan to test antibody concentration in breastmilk? Yes/No? If yes, describe
C16.2 Is there a plan to determine the effect of vaccine on breast-feeding infants? Yes/No? If yes, describe
C16.3 Describe any plans for adverse event evaluation in breast-feeding women
C16.4 What AEFIs should be monitored in breastfed infants?
C16.5 What outcomes of special interest (AESIs) should be monitored in breastfed infants?
C17. Fetus- infant-specific questions
C17.1 Is there a plan to determine if infant seroprotection is achieved following maternal immunization? Yes/No. If no, why? If yes, describe
C17.2 What is the ratio of maternal-to-infant antibody at delivery? (transplacental antibody passage)
C17.3 What is the duration of maternally-derived antibody?
C17.4 What is the effect of maternal antibody on natural disease in the infants?
C18. Adverse events in infants
C18.1 What AEFIs should be monitored in infants?
C18.2 What AESIs should be monitored in infants?
C19. Follow-up infants of after birth
C19.1 How long should infants exposed in utero be followed up after birth?

Section D. Key questions for post-licensure safety evaluation of vaccine use during pregnancy

D1 Who has access to detailed and timely post-licensure safety surveillance data?
D2 General safety surveillance
D2.1 What study designs should be considered for the post-licensure assessment of vaccine safety, in addition to routine surveillance?
D2.2 Are hospital-based systems or sentinel site-based approaches for safety surveillance feasible?
D2.3 Is it feasible to do prospective safety studies of vaccinated pregnant and breast-feeding women?
D2.4 Is it feasible to do retrospective safety studies of vaccinated pregnant and breast-feeding women?
D2.5 How should passive safety surveillance systems be strengthened to improve signal detection?
D2.6 What active safety surveillance approaches should be used to identify AESIs in LMICs?
D3 Safety data for pregnant women exposed to approved or licensed vaccine
D3.1 Was the vaccination recommended by a healthcare provider?
D3.2 Details of vaccine administration: date, platform, construct, adjuvant (See sections B and C)
D3.2.1 In what setting was the vaccine administered?
D3.3 Are there any known adverse events associated with use of the platform, construct, or adjuvant? If yes, give details
D3.4 When did vaccine exposure occur during pregnancy?
D3.5 Can maternal data be linked to the offspring's data and any adverse outcomes in the newborn or neonate?
D3.6 Can maternal data be linked to the offspring's data and any adverse outcomes in the infant (12 months after birth)?
D4 AEFIs and AESIs
D4.1 What pregnancy-specific or neonate-specific AEFIs or AESIs should be monitored?
D4.2 What safety outcomes or potential AEFIs were identified during pre-clinical studies that should be assessed in the post-licensure period?
D4.3 Were any pregnancy-related safety signals identified during previous vaccine clinical trials, either those that recruited pregnant women, or those monitoring inadvertently exposed pregnant women?
D4.4 What patient factors are important for the study population?
D4.4.1 Examples: age; current or prior infections; HIV status; obesity; hypertension; diabetes; alcohol abuse; substance abuse; singleton versus multiple pregnancy; prior pregnancy complications; other factors?
D4.4.2 Is prior infection a factor? Or an exclusion criterion?
D4.4.3 Other factors?
D5 Pregnancy registries
D5.1 Is/was there a pregnancy registry from prior use of candidate vaccine for other indications?
D5.2 Is a post-licensure pregnancy registry in the development plan?
D5.3 Will /was a pregnancy registry mandated by regulatory agencies?
D5.4 Will the manufacturer be able to set up a pregnancy registry in LMICs?
D5.5 Are there plans for the use of standardized and harmonized methods for a pregnancy registry to allow data pooling?
D6 Active post-licensure studies
D6.1 Are pharmacoepidemiology studies planned or established to identify or evaluate potential risks during the post-licensure period?
D6.2 Are there any other ongoing studies following-up on pregnant or breast-feeding women and their infants for 6 to 12 months post-exposure to vaccination?
D6.3 What other safety activities are/were recommended by regulatory authorities or WHO?
D7 Communication of safety findings
D7.1 How will the findings of any safety studies be communicated to pregnant women?
D7.2 How will the findings of any safety studies be communicated to the public?
D7.3 How will the findings of any safety studies be communicated to other key stakeholders?
D7.4 Do the communication plans include advice on how to deal with misinformation and hesitancy due to vaccine safety concerns?
D8 Vaccine uptake
D8.1 What is the anticipated or known acceptance of the vaccine in the general population?
D8.2 What is the anticipated or known acceptance of vaccines in general in pregnant women?

(*continued on next page*)

Table 1 (*continued*)

D8.3	What is the anticipated or known acceptance of the specific vaccine in pregnant women?
D8.4	Will pregnant women choose to participate in vaccine clinical trials?
D8.5	Will pregnant women choose to participate in post-licensure vaccine studies?

Section E. Summary of the evaluation of the candidate vaccine for use in pregnant and breast-feeding women	
E1 Key criteria to suggest vaccine for:	
E1.1	Pregnant women
E1.2	Breast-feeding women
E2 Key criteria to reject vaccine for:	
E2.1	Pregnant women
E2.2	Breast-feeding women
E3 Key considerations for proceeding with evaluation of a vaccine for:	
E3.1	Pregnant women
E3.2	Breast-feeding women
E4 What safety data are needed for inclusion of pregnant women in clinical studies?	
E5 What efficacy data are needed for inclusion of pregnant women in clinical studies?	
E6 What are the identified data gaps?	
E7 In which vaccine development phase should pregnant women be included?	
E8 What is the optimal timing for vaccination during pregnancy?	
E9 Has the communication plan been finalized and accepted by all stakeholders?	
E9.1	Has the communication plan been implemented?

[*] It may be difficult to identify if the reason for hospitalization was for the pregnancy or for the illness.
[**] The threshold for admission to intensive care is likely to be lower for pregnant women than non-pregnant women.

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Disclaimer

The findings, opinions, conclusions, and assertions contained in this consensus document are those of the individual members of the COVAX-CEPI and CEPI-SPEAC Maternal Immunization Working Groups. They do not necessarily represent the official positions of any participant's organization (e.g., government, university, or corporations) and should not be construed to represent any Agency determination or policy.

Funding

This work was supported by funding from the Coalition for Epidemic Preparedness Innovations (CEPI) to the Safety Platform for Emergency vACcines (SPEAC) Project.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Flor M. Munoz reports a relationship with Pfizer that includes: consulting or advisory and funding grants. Flor M. Munoz reports a relationship with Moderna that includes: consulting or advisory. Flor M. Munoz reports a relationship with Meissa Vaccines that includes: consulting or advisory. Flor M. Muno reports a relationship with National Foundation of Infectious Diseases that includes: board membership. Clare L. Cutland reports a relationship with Bill & Melinda Gates Foundation that includes: funding grants. Clare L. Cutland reports a relationship with Pfizer that includes: funding grants. Clare L. Cutland reports a relationship with German Society for International Cooperation (GIZ) GmbH that includes: funding grants. Helen Marshall reports a relationship with Sanofi Pasteur that includes: funding grants. Helen Marshall reports a relationship with Seqirus that includes: funding grants. Helen Marshall reports a relationship with Moderna that includes: funding grants. Helen Marshall reports a relationship with ILiAD Biotechnologies that includes: funding grants. Geeta Swamy reports a relationship with Pfizer that includes: consulting or advisory. Geeta Swamy reports a relationship with GSK that includes: consulting or advisory and speaking and lecture fees. Geeta Swamy reports a relationship with Moderna that includes: consulting or advisory. Geeta Swamy reports a relationship with Sanofi Pasteur that includes: speaking and lecture fees. Corresponding author is an associate editor for Vaccine and a member of the ACOG Immunization Expert Group-FMM Co-author was a member of the Brighton Collaboration Scientific Committee 2018–2023-CLC Co-author is a contributor to UpRoDate on listeria in pregnancy and a Medscape educational contributor on congential CMV - GS. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to acknowledge medical writing and editorial services provided by Margaret Haugh, PhD, MediCom Consult (France) funded by CEPI/SPEAC, and the project management support provided by BMGF and by Izidora Skracic, MSc, and Maria de la Paz Aguirre, MSc, WeDo Project Intelligence Made Easy (Spain), also funded by CEPI/SPEAC.

Appendix A. Appendix

A.1. Members and workstreams of the COVAX-CEPI maternal immunization working group

Co-chairs: Flor Munoz, Ajoke Sobanjo-ter Meulen

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Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.127513.

Data availability

No data was used for the research described in the article.

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