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 Are pregnant women at greater risk of infection-related complications compared with non-pregnant women of child-bearing age?
A1.3 What are the clinical manifestations of disease in pregnant women?
A1.4. Are the clinical manifestations similar to those in non-pregnant women of child-bearing age?
A1.5 Are pregnant women at greater risk of severe disease (e.g. intensive care admission, death) than non-pregnant women and the general population?
A1.6 Is the hospitalization rate higher in pregnant women compared with non-pregnant women and the general population?
A1.7 Is the intensive care admission rate higher in pregnant women compared with non-pregnant women and the general population?
A1.8 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?
A1.9 Are there any disease effects or complications that are specific to pregnant women?
A1.10 Is the risk of infection higher during a specific gestational trimester?
A1.11 Is the risk of severe disease higher during a specific gestational trimester?
A1.12 Is the risk of maternal death higher during a specific gestational trimester?

Section A. Key questions about the pathogen, disease, and pregnancy
A1.13 Are there known maternal factors or underlying medical conditions that increase the risk of infection, severe disease, or death?
A1.14 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?
A2.5 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?

Section A. Key questions about the pathogen, disease, and pregnancy
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?

Section A. Key questions about the pathogen, disease, and pregnancy	
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?

Section A. Key questions about the pathogen, disease, and pregnancy
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?

Section A. Key questions about the pathogen, disease, and pregnancy	
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?

* 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

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

Section B. Key questions about specific vaccine platforms 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.

Section B. Key questions about specific vaccine platforms and components
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?

Section B. Key questions about specific vaccine platforms and components
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

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
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)
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?

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**
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.

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	
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.

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**
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)

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
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?

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
C14.3 Can the full dose series be completed during pregnancy?
C14.4 Can the dose series include pre- or post-pregnancy administration?
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

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
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

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

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