



**COVAX Maternal Immunization Working Group
EXECUTIVE SUMMARY REPORT**

January 2021

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Table of Contents

ABBREVIATIONS4

I. Background5

 I.1 COVID-19 and Pregnant Women5

 I.2 COVID-19 Vaccines and Pregnancy5

II. The Maternal Immunization Working Group6

III. Scope of work7

IV. Project Objectives7

V. Approach7

VI. Outputs7

 V.1 Vaccine candidate mapping, key characteristics, and development timelines.....7

 V.1.1 *Vaccine Development Details at a Glance*8

 V.1.2 *Key Characteristics for Maternal Vaccines for COVID-19 WHO TPP*.....9

 V.2 Key questions for the evaluation of COVID-19 vaccine candidates in pregnant and lactating women.....9

 V.3 Key Questions for the post-licensure safety evaluation of COVID-19 vaccine candidates in pregnant and lactating women.16

 V.4 Summary of Key Questions18

VII. Maternal Immunization Working (MI WG) Group Next Steps19

VIII. COVAX MI WG Interim Report Summary19

APPENDICES

 Appendix I. MI WG composition22

 Appendix II. COVID-19 Vaccine Candidate Mapping.....23

 Appendix III. Key Characteristics for COVID-19 WHO TPP.....24

REFERENCES26

List of Abbreviations and Acronyms

ACIP - CDC Advisory Committee on Immunization Practices
 ACOG - American College of Obstetrics and Gynecology
 ACT - Access to COVID-19 Tools (ACT) Accelerator
 AE – Adverse Event
 AEFI – Adverse Event Following Immunization
 AESI – Adverse Event of Special Interest
 AIDS – Acquired Immunodeficiency Syndrome
 CDC – U.S. Centers for Disease Control and Prevention
 CIOMS - Council for International Organizations of Medical Sciences
 CMI – Cell-mediated immunity
 COVAX – COVID vaccine arm of the Access to COVID-19 Tools Accelerator
 CSL – Biotechnology Company
 DART – Developmental and Reproductive Toxicology
 DSMB – Data Safety Monitoring Board
 EUA/EUL – Emergency Use Authorization (FDA) / Emergency Use Listing (WHO)
 FDA - U.S. Food and Drug Administration
 GSK – GlaxoSmithKline pharmaceutical company
 HIC – High Income Country
 ICU – Intensive Care Unit
 IMPRINT - Immunizing Pregnant Women and Infants Network
 influenza A/H1N12009pdm – strain of influenza virus
 IVAC/JHPIEGO – International Vaccine Access Center of the Johns Hopkins Program
 for International Education in Gynecology and Obstetrics
 LMICs – Low-Middle Income Countries
 MI – Maternal Immunization
 MIS-A – Multisystem inflammatory syndrome in adults
 MIS-C – Multisystem inflammatory syndrome in children
 mRNA – Messenger RNA
 NAM - U.S. National Academy of Medicine
 NIH – U.S. National Institutes of Health
 PCR – Polymerase chain reaction in DNA testing
 PREVENT - Pregnancy Research Ethics for Vaccines, Epidemics, and new Technologies
 RSV – Respiratory Syncytial Virus
 SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2; virus causing COVID-19
 Th1 and Th2 – T lymphocyte helper cells types 1 and 2
 TPP - Target Product Profiles
 VAED – Vaccine-associated enhanced disease
 VVM- Vaccine vial monitor
 WG – Working Group
 WHO - World Health Organization
 WS – Work Stream

I. BACKGROUND

I.1. COVID-19 AND PREGNANT WOMEN

Globally, an estimated 213 million pregnancies occur annually.¹ Pregnant and lactating women make up a significant portion of the frontline global workforce. Among the health care workforce in the United States (U.S.) there are over 300,000 women who are pregnant or lactating at any given time. This proportion is likely higher in low and middle-income countries (LMICs), with higher reproductive rates and longer duration of breast feeding. Health care related occupations are critical to the pandemic response and have been prioritized for COVID-19 vaccine allocation.² Further, women are often employed in occupations that may be associated with potentially high SARS-CoV-2 exposure risk such as public-facing and hospitality workers, teachers, childcare providers, and caregivers. COVID-19 immunization strategies for pregnant and lactating women who rely on employment in these high-risk occupations are therefore urgently needed.

In December 2020, the U.S. National Center for Immunization and Respiratory Diseases updated its “Clinical considerations for use of Pfizer-BioNTech COVID-19 vaccine”³ based upon the US Federal Drug Administration (FDA) and Advisory Committee on Immunization Practices (ACIP) review of data submitted for Emergency Use Authorization. While the company data on pregnancy was “insufficient to inform vaccine-associated risks in pregnancy,”⁴ the interim guidelines report that “observational data demonstrate that while the absolute risk is low, pregnant people with COVID-19 have an increased risk of severe illness, including illness resulting in Intensive Care Unit (ICU) admission, mechanical ventilation, or death. Additionally, they might be at an increased risk of adverse pregnancy outcomes, such as preterm birth.⁵ Several studies have identified these higher risks of complications^{6,7,8} and deaths^{9,10,11} when comparing pregnant women with non-pregnant women with COVID-19. Similar to the general population, severe disease appears to be more common among pregnant women who are older (36-44 years), or who have underlying medical conditions, such as obesity,^{12,13,14} gestational diabetes, and hypertension.^{15,16}

Data from high income countries (HICs) suggest that adverse birth outcomes, such as preterm delivery, are more common among pregnant women infected with SARS-CoV-2, particularly if they are infected in the third trimester.^{17,18,19} Newborns who test positive for COVID-19 are usually born to mothers who tested positive less than one week prior to delivery.²⁰ Most are asymptomatic or have mild infection and some may require a short stay in neonatal intensive care. Vertical transmission appears to be rare.^{21,22}

Observational studies from the US and the United Kingdom report that Black and Hispanic women who are pregnant appear to be disproportionately at risk of severe disease and hospitalization.^{23,24} Little or no pregnancy-specific data is available from LMICs largely due to a lack of data collection infrastructure and forethought. Additional data will be needed to inform local decision-making on the administration of SARS-CoV-2 vaccines to pregnant and lactating women.

I.2 COVID-19 VACCINES AND PREGNANT WOMEN

The Council for International Organizations of Medical Sciences (CIOMS) guidelines encouraged the inclusion of pregnant women in clinical studies in 2002,²⁵ followed by the United Nations AIDS/World Health Organization in 2005.²⁶ Most recently, the U.S. Food and Drug Administration (FDA) published its support for the inclusion of pregnant women in a draft guidance for the pharmaceutical industry.²⁷ These organizations recognize that the exclusion of pregnant women from clinical trials can lead to a lack of data with which they, their families, and their health care providers can make informed decisions about the potential benefits and risks of medications and vaccines administered during pregnancy. In the 2020 “Development and Licensure of Vaccines to Prevent COVID-19” guidance,²⁸ FDA encourages vaccine sponsors 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.” Despite advocacy for the inclusion of pregnant and lactating people in clinical trials, pregnant women were not included in the clinical studies of the COVID-19 vaccines currently approved for

emergency use. According to several reports, “studies in pregnant women are planned.”^{29,30} Data from animal studies (developmental and reproductive toxicity studies) are anticipated to be shared shortly and, according to the American College of Obstetricians and Gynecologists (ACOG), “there have not been any major safety signals identified.”³¹

Vaccines for pregnant women are one of the most important public health measures undertaken globally to reduce the burden of tetanus, pertussis and seasonal influenza in mothers and infants. During previous respiratory pathogen pandemics, such as influenza A/H1N12009pdm, infection in pregnant women has been associated with an increased risk of severe disease and hospitalization, and pregnant women have subsequently been prioritized for immunization.^{32,33}

Various organizations, including the U.S. National Academy of Medicine (NAM),³⁴ the American College of Obstetrics and Gynecology (ACOG),³⁵ the Pregnancy Research Ethics for Vaccines, Epidemics, and new Technologies (PREVENT) group,³⁶ the Society for Maternal-Fetal Medicine,³⁷ and the World Health Organization (WHO)^{38,39} support the position that pregnant and lactating women are a priority population that must not be excluded from the COVID-19 vaccine allocation strategy.

On December 12, 2020, guidelines for the immunization of pregnant and lactating women were included in the CDC COVID-19 vaccine allocation guidance⁴⁰ which can be summarized as follows:

- There are no safety or efficacy data available from clinical experience with pregnant women but studies including pregnant women are planned. Animal studies are being conducted, results should be publicly available from some manufacturers soon, and no major safety signals have been reported.
- Observational studies have suggested that pregnant women may be at an increased risk for severe disease, ICU intervention, and death. Preterm birth has been identified as a potential risk. Underlying medical and sociological conditions may increase the risk for adverse outcomes.
- mRNA vaccines are not live vaccines, they are degraded quickly by normal cell processes and vaccine RNA does not enter the cell nucleus – therefore, the vaccine cannot cause genetic defects in infants and is not thought to be risk to a breastfeeding child.

- Pregnancy and breastfeeding are not considered to be contraindications to COVID-19 immunization. If pregnant or lactating persons are part of a group that is recommended to receive the vaccine, they may choose to be vaccinated.
- Pregnant women who experience fever following vaccination should be counseled to take acetaminophen as fever has been associated with adverse pregnancy outcomes.

On December 13, 2020, ACOG published a Practice Advisory for their members which states, in agreement with the CDC and ACIP, that COVID-19 vaccines should not be withheld from pregnant or lactating individuals who meet criteria for vaccination based on ACIP-recommended priority groups. They add that “individuals who decline vaccination should be supported in their decision.”⁴¹

II. THE MATERNAL IMMUNIZATION WORKING GROUP

In April 2020, in response to the COVID-19 pandemic, the Access to COVID-19 Tools (ACT) Accelerator,⁴² a global collaboration, was launched to facilitate the development, production, and equitable access to COVID-19 tests, treatments, and vaccines. The ACT Accelerator’s SARS-CoV-2 vaccine research, development, and manufacturing workstream comprises a Clinical Development and Operations SWAT team to identify tools and support for vaccine developers to facilitate COVID-19 vaccine licensure. Recognizing the importance of addressing the needs of pregnant and lactating women during the COVID-19 pandemic, the SWAT team established the COVAX COVID-19 Maternal Immunization Working Group (MI WG) in August 2020.

The COVAX MI WG, co-chaired by Drs. Flor M. Munoz (Baylor College of Medicine) and Ajoke Sobanjo-ter Meulen (Bill & Melinda Gates Foundation) invited a selected, inclusive group of professionals with expertise in various aspects pertinent to maternal immunization, who represent diverse organizations, geographies, and settings, to broadly contribute to the objectives of the working group. The MI WG is comprised of members from various disciplines including academia, regulatory, medicine, ethics, clinical research,

industry, pharmacovigilance, and vaccine safety [see [WG Composition, Appendix I](#)]. Members of the MI WG are contributing at many levels including via relevant maternal immunization projects such as WHO's multi-country study on maternal immunization safety surveillance,⁴³ IVAC/JHPIEGO's project on COVID-19 maternal immunization implementation preparedness,⁴⁴ the National Institutes of Health (NIH) Operation Warp Speed,⁴⁵ Infectious Diseases Clinical Research Consortium (IDCRC),⁴⁶ Immunizing Pregnant Women and Infants Network (IMPRINT),⁴⁷ and industry efforts to advance maternal vaccines through clinical development.

The aim of the COVAX Maternal Immunization Working Group (COVAX MI WG) is to enable the evaluation and utilization of COVID-19 vaccine candidates suitable for use in pregnant and lactating women, given their need for access to safe and effective vaccines to counter COVID-19-related morbidity and mortality.

III. SCOPE OF WORK

The COVAX MI WG's scope of work consists of 1) the identification of research and development needs towards a COVID-19 vaccine recommendation for pregnant women, and 2) the alignment of the tasks and objectives of the COVAX MI Working Group with global efforts towards the evaluation and implementation of COVID-19 vaccines for maternal immunization.

IV. PROJECT OBJECTIVES

The overarching goal of the COVAX MI WG is to support the availability of at least one COVID-19 vaccine candidate that is suitable for use in pregnant and lactating women. To accomplish this goal, the COVAX MI WG set out to 1) describe approaches for the evaluation of COVID-19 vaccine candidates for use in pregnant women and their infants, from pre-licensure clinical studies to the post-licensure period; 2)

create an evaluation framework for COVID-19 vaccine candidates for use in pregnant and lactating women; and 3) describe the necessary data and studies to close the availability and access gap to safe and effective COVID-19 vaccination and prevention strategies for pregnant and lactating women.

V. APPROACH

In order to cover relevant issues pertaining to the inclusion of pregnant women across the vaccine development pathway ranging from the pre-clinical through the post-approval phase, the Working Group chairs created three workstreams to address key questions related to 1) Vaccine Candidate Mapping, 2) Pre-clinical and Clinical Evaluation, and 3) Vaccine Safety, as shown in [Box 1](#). On an ad hoc basis, workstream leads and members also solicited input from external subject matter experts. The Working Group's ethics and regulatory advisors served to review and advise across all workstream deliberations and outputs. During weekly or bi-weekly meetings, workstream representatives shared group findings and identified areas of consensus to refine and address their key questions. This process resulted in workstream outputs and deliverables that were shared among the working group for additional input.

VI. OUTPUTS

V.1 VACCINE CANDIDATE MAPPING, KEY CHARACTERISTICS, AND DEVELOPMENT TIMELINE

The eleven COVID-19 vaccine candidates prioritized by COVAX and their stages of development are shown in the vaccine candidate mapping in [Appendix II](#). The working groups developed a dynamic, candidate-specific, product

map indicating key components, clinical development status, timeline to approval and other relevant characteristics for their potential use in pregnant women.

V.1.1 Vaccine development details at a glance

The vaccine candidate vignettes developed by the COVAX MI WG provide a visualization of the vaccine candidate's progress along the clinical development path.

BOX 1. Workstream Responsibilities and Methods

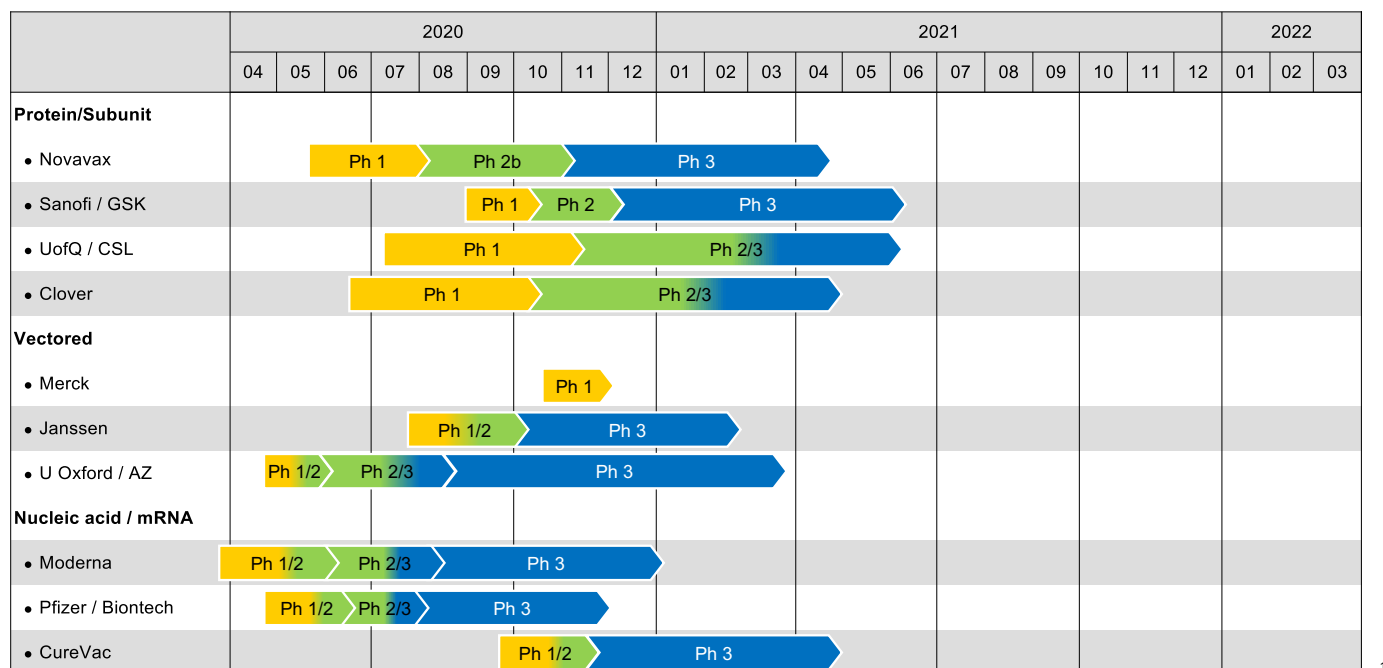
Workstream 1. Vaccine Candidate Mapping / Key Characteristics – Lead: Dr. Emily Erbelding, US NIH
<ul style="list-style-type: none"> ▪ Review of COVID-19 vaccine candidates ▪ Expert consultations ▪ Summary of key characteristics of COVAX supported COVID-19 vaccine candidates and data mapping as pertinent to maternal immunization
Workstream 2. Pre-clinical / Clinical Data – Lead: Prof. Beate Kampmann, LSHTM
<ul style="list-style-type: none"> ▪ Identification of key questions and data needs for the pre-clinical and clinical assessment of vaccine candidates for maternal immunization ▪ Discussion forum with invited presentations and expert consultations to inform the WG on various topics including burden and impact of COVID19 in pregnancy, placental physiology, the fetus and newborn, clinical development, ethics, and regulatory considerations. ▪ Survey of work group members on key questions with collection and evaluation of responses. ▪ Discussion and consensus among the full Working Group
Workstream 3. Vaccine Safety – Leads: Prof. Andy Stergachis, Univ of Washington; Dr. Steve Anderson, US FDA
<ul style="list-style-type: none"> ▪ Identification of pregnancy safety considerations for four vaccine development scenarios: <ul style="list-style-type: none"> ▪ Pregnant women not included in pre-licensure clinical trials, i.e., excluded from clinical trials. ▪ Pregnant women included in pre-licensure clinical trials. ▪ Separate pre- (or post-) licensure clinical trial specifically designed for pregnant women. ▪ Post-licensure safety surveillance ▪ Review and consideration of key regulatory and WHO guidance documents pertaining to pregnancy safety studies ▪ Development and administration of a survey of the Advisory Board members of the project, “Sentinel Site Readiness for Maternal Immunization Active Safety Surveillance in LMICs (Lead: Prof. Pierre Buekens, Tulane University),” with collection and evaluation of written responses.
Cross-cutting Workstreams:
<ul style="list-style-type: none"> ▪ Review and input from ethics and regulatory experts across all work streams

At the same time, they allow an estimation of the potential timing of including pregnant women in the development path. There vignettes can be updated as additional information becomes available and are supplemented by the WG's evaluation and

identification of additional data and studies that are needed to close the gap between approval and administration to pregnant women. The summary development timeline is shown in [Figure 1](#) and individual vaccine vignettes are available by clicking on the slide.

Figure 1.
Summary slide: projected availability of COVID-19 vaccines prioritized by COVAX

Summary: COVID-19 Vaccines prioritized by COVAX – Estimated Timelines and Availability for Pregnant Women (Projected timelines as of October 2020 based on public existing and planned studies)



Note: Double click anywhere on slide to access individual vignettes with live links.

V.1.2. Key Characteristics for Maternal Vaccines Annex

WHO formulated a Target Product Profile⁴⁸ (TPP) that describes the preferred and the minimally acceptable characteristics desired in a vaccine candidate, particularly in those for long term protection of persons at high risk of acquiring, or developing an acute response to, COVID-19. To help facilitate the evaluation of COVID-19 vaccine candidates that may be suitable for use in pregnant and lactating women, the COVAX MI WG developed key characteristics for maternal vaccines for COVID-19. To complement the WHO TPP, these key characteristics for a maternal vaccine likewise focus on minimum and optimistic variables for pregnant and lactating women [Key Characteristics for Maternal Vaccines for COVID-19 TPP, Appendix III].

V.2 KEY QUESTIONS FOR THE PRECLINICAL AND CLINICAL EVALUATION OF VACCINE CANDIDATES FOR PREGNANT AND LACTATING WOMEN

Key questions for the evaluation of any COVID-19 vaccine's potential for use during pregnancy and lactation were developed by the COVAX MI WG and are shown below [Table 1. Sections A through E]. The key questions for the assessment of the suitability of vaccine candidates for pregnant and lactating women will support COVAX's goal of identifying at least one vaccine for pregnant and lactating women. Guidance from the COVAX-MI WG based on these key questions will follow in the full project report.

The key questions serve as an evaluation framework for all stages of COVID-19 vaccine development across the different vaccine platforms. The table is organized in sections focusing on the various intersecting issues that comprise the evaluation of vaccine use in pregnant women:

Section A. Key Questions on the Pathogen (SARS-CoV-2), Disease (COVID-19), and Pregnancy

Section B. Questions on Specific Vaccine Platforms and Characteristics (based on the Brighton Collaboration BRAVATO vaccine platform modules)

Section C. Key Questions on Development and Planning for All Candidate Vaccines for Pregnant and Lactating Women and their Exposed Offspring

Section D. Key Questions for Post-Licensure Safety Evaluation of COVID-19 Vaccine Use During Pregnancy

Section E. Summary of Key Questions for COVID-19 Vaccine Use During Pregnancy and Lactation

Table 1. Section A addresses the information needed to evaluate the effect of the pathogen (SARS-CoV-2), and the disease (COVID-19) on pregnant and lactating women.

Table 1. Key Questions for the Evaluation of COVID-19 Vaccine Candidates for Pregnant and Lactating Women

Table 1. Section A.

COVAX Maternal Immunization Working Group
Section A. Key Questions on the Pathogen (SARS-CoV-2), Disease (COVID-19), and Pregnancy
A.1 What is known of SARS-CoV-2 and COVID-19 effects during pregnancy
1.1 Are pregnant women at greater risk of SARS-CoV-2 infection?
1.2 What is the infection rate in pregnant women compared to non-pregnant women/population?
1.3 What are the clinical disease manifestations of COVID-19 in pregnant women?
1.4 Are pregnant women at greater risk of severe disease compared to non-pregnant women/population?
1.5 Is the rate of hospitalization greater in pregnant women compared to non-pregnant women/population?
1.6 Is the rate of intensive care admission greater in pregnant women compared to non-pregnant women/population?
1.7 Is the risk of maternal death during pregnancy greater than in non-pregnant women/population?
1.8 Are there disease effects or complications specific to pregnant women?
1.9 Is there a greater risk of infection in a specific trimester of gestation?
1.10 Is there a greater risk of severe disease during a specific trimester of gestation?
1.11 Is there a greater risk of maternal death in a specific trimester of gestation?
1.12 Are there known maternal factors or underlying medical conditions that increase the risk of infection, severe disease or death?
1.13 What factors or underlying medical conditions increase the risk of SARS-CoV-2 infection, severe COVID-19 disease, or death during pregnancy?
1.14 What are other potential effects of SARS-CoV-2 infection and disease in pregnancy?
1.15 Are there available safe and effective SARS-CoV-2 antiviral or other specific treatments for pregnant women?
1.16 What is the efficacy of existing therapies in pregnant women?
1.17 Are pregnant women included in clinical trials of SARS-CoV-2 treatments and vaccines?

A.2. Pregnancy and Obstetric outcomes:
2.1 What are the adverse obstetric outcomes associated with maternal SARS-CoV-2 infection and disease?
2.2 What is the risk of preterm labor in infected vs. non-infected women?
2.3 What is the risk of preterm delivery in infected vs. non-infected women?
2.4 What is the rate of C-section delivery in infected vs. non-infected women?
2.5 What are the indications for C-section delivery in infected women?
2.6 What is the risk of specific maternal obstetric complications associated with SARS-CoV-2 infection and disease during pregnancy, including:
2.6.1 Hypertension disorders, eclampsia, preeclampsia
2.6.2 Gestational diabetes
2.6.3 Antenatal and perinatal bleeding
2.6.4 Chorioamnionitis
2.6.5 Maternal infection and sepsis
2.6.6 Post-abort and post-partum endometritis
A.3. Is there evidence of Vertical Transmission of SARS-CoV-2:
3.1 Via placenta? Describe evidence, if any
3.2 Via breastmilk? Describe evidence, if any
3.3 Is there evidence of placental infection with SARS-CoV-2?
3.3.1 If yes, what are the mechanisms of placental infection?
3.4 Is there evidence of transplacental transfer of antibodies to SARS-CoV-2?
3.5 Is there evidence of transfer of antibodies to SARS-CoV-2 via breast milk?
A.4. Fetuses:
4.1 Does fetal infection occur?
4.2 What is the risk of fetal infection?
4.2.1 What is the risk of fetal infection by trimester of gestation?
4.2.2 Is there evidence of teratogenicity/congenital malformations from infection?
4.3 What is the risk of teratogenicity?
4.4 Is there a risk of fetal loss?
4.5 Is there a risk of fetal loss by trimester of gestation?
4.6 What is the risk of spontaneous abortion/miscarriage?
4.7 What is the risk of stillbirth?
4.8 What is the risk of intrauterine growth restriction?
4.9 Are there other fetal effects/risks associated with maternal infection with SARS-CoV-2?
A.5 Neonates and Infants:
5.1 What is the risk of prematurity with SARS-CoV-2 infection?
5.2 What is the risk of neonatal SARS-CoV-2 infection?
5.3 What is the mechanism of transmission of neonatal infection from mother to infant?
5.4 What are the clinical manifestations of neonatal infection?
5.5 What is the risk of severe neonatal disease?
5.6 What is the risk of neonatal death?
5.7 What is the risk of neonatal sepsis, meningitis, and other infections?
5.8 What is the risk of infection, disease, and death in the first 6 months of life?
5.9 What is the risk of infection, disease, and death in the first year of life?

A.6 Post-partum and Lactating Women:
6.1 Are post-partum and lactating women at greater risk of SARS-CoV-2 infection?
6.2 What is the SARS-CoV-2 infection rate in post-partum and lactating women compared to non-pregnant and non-lactating post-partum women population?
6.3 Are post-partum and lactating women at greater risk of severe COVID-19 disease compared to non-pregnant and non-lactating post-partum women?
6.4 Is the rate of hospitalization from COVID-19 greater in post-partum and lactating women compared to non-pregnant and non-lactating women?
6.5 Is the rate of intensive care admission greater in post-partum and lactating women with COVID-19 compared to non-pregnant and non-lactating post-partum women?
6.6 Is the risk of maternal death from COVID-19 during post-partum period greater than in the non-pregnant population?
6.7 Is the risk of maternal death from COVID-19 greater in lactating women than non-lactating women?
6.8 Are there complications from COVID-19 specific to post-partum and lactating women?
6.9 Are there available antiviral or other specific therapies for post-partum and lactating women?
6.10 What is the efficacy of available treatments in post-partum and lactating women?
6.11 Are post-partum and lactating women included in clinical trials of treatments and vaccines?

Section B, which focuses on vaccine platform characteristics, was developed to harmonize with existing tools developed by the Brighton Collaboration BRAVATO⁴⁹ project to assess the characteristics of specific vaccine platforms, including nucleic acid vaccines,⁵⁰ vector-based vaccines,⁵¹ protein/subunit-based vaccines,⁵² inactivated virus vaccines,⁵³ and live virus vaccines.⁵⁴ The specific Brighton Collaboration templates can

be found by double-clicking the links in Table 1. Section B.2. When pertinent, data collected through Brighton Collaboration tools can be complimented by the COVAX MI WG Key Questions in Table 1 to inform the evaluation of COVID-19 candidate vaccines for use by pregnant and lactating women ([Table 1, Sections B-E](#)).

Table 1. Section B.

Section B. Questions on Specific Vaccine Platforms and Components
B.1 Vaccine name and Manufacturer
B.2 Vaccine Construct/Platform (use BRAVATO tables for specific non-pregnancy questions)
<ul style="list-style-type: none"> ▪ Protein vaccines ▪ Nucleic acid (RNA and DNA) vaccines ▪ Viral vector vaccines ▪ Live-attenuated viral vaccines ▪ Inactivated viral vaccines
B.3 General and pre-clinical toxicology studies on vaccine construct and components
3.1 Are there safety data from animal models (pregnant/non-pregnant) with the vaccine construct/platform or any of the vaccine components?
<p>3.1.1 Have Developmental and Reproductive Toxicity Studies (DART) been conducted? Describe studies and what component of the vaccine was evaluated (complete vaccine construct or specific components)</p> <p>3.1.2 If yes, are there any identified developmental or reproductive toxicities? If yes, describe.</p> <p>3.1.3 Are there any other pregnancy-related issues in animal studies associated with any of the specific components of this vaccine? If yes, describe.</p>
3.2 Are there placental biology data for this vaccine's construct/platform or components? Describe.
B.4 Construct/Platform-specific questions
4.1 Are there pregnancy-related issues in clinical studies associated with any of the specific construct/ platform of this vaccine? If yes, describe.

B.5 Antigen, adjuvant and other components-specific questions
5.1 Are there pregnancy-related issues in clinical studies associated with any of the antigen, adjuvant or other specific components of this vaccine? If yes, describe.
B.6 Construct/Platform-specific data in humans: non-pregnant population
6.1 Are there safety data from already licensed vaccines that use this specific platform or construct in non-pregnant populations? Describe
6.2 Are there safety data from clinical trials using this specific platform or construct in non-pregnant populations even if not licensed? Describe
B.7 Construct/Platform-specific efficacy data in humans: non-pregnant population
7.1 Describe mechanism/correlates of protection
7.2 Are there efficacy data from clinical trials using this specific vaccine in non-pregnant populations even if not licensed? Describe
B.8 Construct/Platform-specific safety data in humans: pregnant populations
8.1 Are there safety data from pregnant women in early clinical studies using this specific vaccine even if not licensed?
8.2 Are there safety data from inadvertently (in or outside clinical trials) exposed pregnant women?
8.3 Are there safety data from lactating women?
8.4 Are there known pregnancy-related safety issues with this specific vaccine?
B.9 Construct/Platform-specific efficacy data in humans: pregnant population
9.1 Describe mechanisms/correlate of protection
9.2 Are there efficacy data from early clinical trials or PK/PD studies using this specific vaccine even if not licensed?
9.3 Are there efficacy data from inadvertently exposed pregnant women?
9.4 Are there efficacy data from lactating women?
9.5 Are there pregnancy-specific efficacy issues with this specific vaccine? If yes, describe.
B.10 Other vaccine components – Pregnancy-specific questions
10.1 What is known about the delivery system (e.g., lipid nanoparticles) or other components in pregnancy?
10.2 What is known about transplacental transfer?
10.3 What is known about permanence of vaccine delivery or other components in tissues?
B.11 Vaccine storage, delivery, and administration characteristics
11.1 Is vaccine utilization in the context of antenatal care feasible?
11.1.1 Describe vaccine storage requirements
11.1.2 Describe vaccine administration requirements
11.1.3 Describe the number of doses needed and intervals between doses
11.1.4 Describe specific considerations for vaccine administration in relation to other vaccines that are given during pregnancy (e.g., Influenza, tetanus, pertussis).
11.1.5 Describe specific considerations for vaccine administration in relation to medications that are or could be given during pregnancy.

Following the evaluation of the characteristics of specific vaccine candidates, the COVAX MI WG developed key questions to be asked of all vaccines that are considered for maternal immunization, regardless of vaccine composition

[Table 1. Section C]. Many of these are generalizable questions that are useful to evaluate immunization safety in candidate vaccines proposed for most infectious diseases.

Table 1. Section C.

Section C. Key Questions on Development and Planning for All Candidate Vaccines for Pregnant and Lactating Women and their Exposed Offspring
C. Vaccine Development Information
C.1. Pre-clinical Pregnancy Data
<p>1.1 Are results of DART studies available or required?</p> <p style="padding-left: 20px;">1.1.1 DART studies date (or target date) of completion</p> <p style="padding-left: 20px;">1.1.2 Findings of DART studies</p> <p>▪ (See also questions in Table 1. Section B.3)</p>
C.2. Clinical Development status and plans for the vaccine in non-pregnant population
<p>2.1 Target populations in clinical studies</p> <p style="padding-left: 20px;">2.1.1 Planned studies: planned total enrollment (answer for each: phase 1, phase 2, phase 3)</p> <p style="padding-left: 20px;">2.1.2 Ongoing studies: planned total enrollment (answer for each: phase 1, phase 2, phase 3)</p> <p style="padding-left: 20px;">2.1.3 Completed studies: total enrollment (answer for each: phase 1, phase 2, phase 3)</p> <p>2.2 Location of clinical studies</p> <p style="padding-left: 20px;">2.2.1 In what countries are/will clinical studies be conducted?</p> <p style="padding-left: 20px;">2.2.2 Will studies be conducted in HIC and LMIC countries simultaneously?</p> <p style="padding-left: 20px;">2.2.3 Will approved vaccines be distributed in HIC and LMIC countries simultaneously?</p> <p style="padding-left: 20px;">2.2.4 Will vaccine be distributed in epidemic and/or endemic areas?</p>
C.3. Safety data from non-pregnant population:
3.1 Vaccine reactogenicity (after each dose)
3.2 Proportion of subjects with fever, frequency, and duration of fever after each immunization, need for preemptive or symptomatic treatment
3.3 Adverse events following immunization (AEFIs)
3.4 Serious adverse events (SAEs)
3.5 Adverse events of special interest (AESIs)
3.6 Duration of safety follow up
C.4. Immunogenicity data from non-pregnant population:
4.1 Is there an accepted correlate of protection? (include assessment of the quality of the data)
4.2 Antibody responses (include assessment of quality of the data)
4.3 Cell mediated immunity (Th1 vs. Th2) responses (include assessment of quality of the data)
4.4 Duration of immunity (include assessment of quality of the data)
4.4.1 How is immunity defined? (antibodies, CMI, Other?)
4.4.2 What is the duration of follow up and protection
4.5 Is there a need for repeated immunization
C.5. What efficacy data are available from non-pregnant population?
5.1 Efficacy after partial vaccination?
5.2 Efficacy after complete vaccination?
C.6. Inadvertent pregnancy exposures in clinical studies in non-pregnant populations
6.1 Is there a plan for the capture of data from women who become pregnant during clinical trials?
6.1.1 Describe plan or protocol, as well as mechanism for reporting outcomes.
6.2 Will women who become pregnant during clinical trials have the option to remain in the trials?
6.2.1 Yes/no: explain rationale and plan.
6.3 What immunogenicity data are being/will be collected from women who become pregnant during clinical trials?
6.3.1 Describe immunogenicity data, if any, collected to date.
6.4 What safety data are being/will be collected from women who become pregnant during clinical trials?
6.4.1 Describe safety data, if any, collected to date.
6.4.2 Include data collection forms and mechanisms for reporting outcomes
6.5 What efficacy data are being/will be collected from women who become pregnant during clinical studies?
6.5.1 Describe efficacy data, if any, collected to date.
6.6 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.

6.7 What is the plan for collection of data from women in the post-partum period? 6.7.1 Describe post-partum data, if any, collected to date.
6.8 What is the plan for follow up and collection of safety and efficacy data in infants of women who become pregnant in clinical trials?
C.7. Communication plan for inadvertent exposures in pregnant women
7.1 What is the plan to analyze and share information from inadvertent pregnancy exposures to vaccine during clinical trials?
C.8. Inclusion of pregnant women in clinical trials
8.1 Is there a plan to extend enrollment of clinical studies to pregnant women? 8.1.1 If no, what is justification for exclusion? 8.1.2 If yes, what is the plan for the recruitment of pregnant women into clinical studies? Describe.
8.2 What safety data are being/will be collected from pregnant women in clinical studies? 8.2.1 Describe safety data, if any, collected to date.
8.3 What immunogenicity data are being/will be collected from pregnant women in clinical studies? 8.3.1 Describe immunogenicity data, if any, collected to date.
8.4 What efficacy data are being/will be collected from pregnant women in clinical studies? 8.4.1 Describe efficacy data, if any, collected to date.
8.5 Is there a plan for the collection of data from women in the post-partum period? If yes, describe, if no, explain.
8.6 Is there a plan for the collection and testing of breastmilk from post-partum women who were enrolled in clinical studies while pregnant? If yes, describe, if no, explain.
8.7 Is there a plan for the collection and follow up of infants of women enrolled in clinical studies while pregnant? Describe protocol, safety, immunogenicity, efficacy data being collected, as well as duration of follow up.
C.9. Communication plan for pregnancy exposures in clinical studies
9.1 What is the plan to analyze and share the information from vaccine administration to pregnant women enrolled in clinical trials?
C.10. Plan for inclusion of lactating women in clinical trials
10.1 Is there a plan to extend clinical studies to lactating women? If yes, describe. If not, what is the justification for their exclusion?
10.2 Is there a plan for the collection and testing of breastmilk from lactating women enrolled in clinical studies? ▪ (See also questions in Table 1. Section C.16)
C.11. Fetuses/neonates/infants:
11.1 What is the plan for capture of data from exposed fetuses of pregnant women enrolled in clinical studies?
11.2 What is the plan for capture of data from exposed neonates whose mothers were enrolled in clinical studies?
11.3 What is the plan for follow-up of exposed infants whose mothers were enrolled in clinical studies? Describe, including intervals and duration.
11.4 Will infant antibody titers be sequentially measured following birth to assess levels and duration after exposure? ▪ (See also questions in Table 1 section C.17.)
C.12. Vaccine approval for pregnant women
12.1 What outstanding data is needed for vaccine approval for pregnant women?
C.13. Pregnancy-specific safety questions
13.1 What reactogenicity is acceptable in pregnancy? 13.1.1 Proportion of subjects with fever, severity of fever, duration of fever 13.1.2 Local reactogenicity 13.1.3 Systemic reactogenicity 13.1.4 Other

C.14. Timing of vaccination during pregnancy
14.1 What should be the preferred timing of vaccination during pregnancy and why?
14.2 Is the dosing schedule amenable to administration during pregnancy?
14.3 Can the full dose series be completed during pregnancy?
14.4 Can the dose series include pre- or post-pregnancy administration?
14.5 Can the dose series be administered with other vaccines given during pregnancy? What are the considerations for concomitant vaccination?
C.15. Adverse events in pregnant women
15.1 What adverse events following immunization (AEFIs) should be monitored? Maternal, Obstetric, Fetal/neonatal
15.2 What outcomes of special interest (AESIs) should be monitored?
15.3 What is the risk of vaccine-associated enhanced disease (VAED)?
15.4 What is the risk of multisystem inflammatory syndrome in adults (MIS-A)?
15.5 What is the risk of obstetric complications?
15.6 What is the risk of neonatal complications? Are infant AEs associated with gestational age and timing of exposure?
C.16. Lactation-specific questions
16.1 Is there a plan to test antibody concentration in breastmilk? Yes/No? If yes, describe.
16.2 Is there a plan to determine the effect of vaccine on lactating infants? Yes/No? If yes, describe.
16.3 Adverse events in lactating women: describe plan for evaluation
16.4 What adverse events following immunization (AEFIs) should be monitored in breastfed infants?
16.5 What outcomes of special interest (AESIs) should be monitored in breastfed infants?
C.17. Fetus/infant-specific questions
17.1 Is there a plan to determine if infant seroprotection is achieved following maternal immunization? Yes/No. Why? If yes, describe.
17.2 What is the ratio of maternal: infant antibody at delivery? (transplacental antibody transfer)
17.3 What is the duration of maternally derived antibody?
17.4 Effect of maternal antibody on natural disease in infants?
C.18. Adverse events in infants:
18.1 What adverse events following maternal immunization (AEFIs) should be monitored?
18.2 What outcomes of special interest (AESIs) should be monitored?
C.19. How long should infants exposed in utero be followed-up after birth?

V.3 KEY QUESTIONS FOR THE POST-LICENSURE SAFETY EVALUATION

Safety evaluation of pharmaceuticals, including vaccines, continues throughout the lifetime of the product. Various methods are employed to continue to collect and evaluate reports of adverse events following immunization (AEFIs). Usually, such activities are mandated as a condition of approval by regulatory agencies. As products are used by the general public under real-world conditions, more information

about unexpected or rare events, as well as rates and risk factors of adverse events, become available for evaluation.

Post-licensure activities are an important component of medical product development. Because pregnant women are actively excluded from most clinical trials, a sufficient level of pregnancy safety information is rarely available at the time of product licensure. Consequently, active surveillance (e.g., pregnancy registries or existing disease and vaccine safety surveillance systems) is an important tool for safety data collection in the post-licensure period because, in part, of its prospective design and the ability to collect detailed patient level data.

Data collected via active surveillance methods and post-licensure studies, e.g., pregnancy registries, and safety monitoring studies in special populations such as healthcare workers, may be required to assess potential serious risks to

the pregnancy that may affect the health of the fetus or the woman due to drug or biological product use during pregnancy. [Table 1. Section D.]

Table 1. Section D.

Section D. Key Questions for Post-Licensure Safety Evaluation of COVID-19 Vaccine Use During Pregnancy	
D.1. Who has access to detailed and timely post-licensure safety surveillance data?	
D.2. General safety surveillance	
2.1	What study designs should be considered for the assessment of vaccine safety in addition to routine surveillance?
2.2	Are hospital-based systems or sentinel site-based approaches for safety surveillance feasible?
2.3	Is it feasible to do prospective safety studies of COVID-19 vaccinated women?
2.4	Is it feasible to do retrospective safety studies of COVID-19 vaccinated women?
2.5	How should passive safety surveillance systems be strengthened for signal detection?
2.6	What active safety surveillance approaches should be used to identify AESIs in LMICs?
D.3. Safety data questions for pregnancy exposures to approved for use or licensed vaccine	
3.1	Was the COVID-19 vaccination recommended by a health care provider?
3.2	Details of vaccine administration, date, platform, construct, adjuvant (See sections B and C)
3.2.1	In what setting was the vaccine administered?
3.3	What, if any, are the known adverse events associated with the use of the platform/construct/adjuvant?
3.4	When during pregnancy did COVID-19 vaccine exposure occur?
3.5	Can a mother be linked to child and any adverse outcomes in the newborn or neonate?
3.6	Can a mother be linked to child and any adverse outcomes in infant (12 months after birth)?
D.4. Adverse Events Following Immunization (AEFIs)/Adverse Events of Special Interest (AESIs)	
4.1	What adverse outcomes or specific pregnancy outcomes or neonate outcomes of special interest (AESIs) should be monitored?
4.2	What safety outcomes or potential adverse events were identified during pre-clinical studies that should be studied post-approval?
4.3	Was any pregnancy related safety signal identified during COVID-19 vaccine previous clinical studies (clinical trials that recruited pregnant women, or those monitoring accidentally exposed pregnant women)?
4.4	What patient factors are important for the study population? <ul style="list-style-type: none"> ▪ Age? ▪ Current or prior infections? ▪ HIV status? ▪ Obesity? ▪ Hypertension? ▪ Diabetes? ▪ Alcohol abuse? ▪ Substance abuse? ▪ Singleton versus multiple pregnancy? ▪ Prior pregnancy complications? Other factors? ▪ Is prior COVID-19 infection a factor? Or an exclusion criterion? ▪ Other factors?
D.5. Pregnancy Registries	
5.1	Is/was there a pregnancy registry from prior use of candidate vaccine for other indications?
5.2	Is a post-licensure pregnancy registry in the development plan?
5.3	Will/was a pregnancy registry mandated by regulatory agencies?
5.4	Will the manufacturer be able to conduct a pregnancy registry in LMICs?

5.5 Are there plans for use of standardized and harmonized methods for a pregnancy registry to allow data pooling?
D.6. Active post-licensure studies
6.1 Are pharmacoepidemiology studies planned or established to identify or evaluate potential risks during the post-licensure period?
6.2 Are there other ongoing studies planned to follow-up on the pregnant or lactating women and their infants for 6 months to a year post-exposure to COVID-19 vaccination?
6.3 What other safety activities are/were recommended by regulatory authorities or the WHO?
D.7. Communication of Safety Findings
7.1 How will the findings of any safety studies be communicated to pregnant women?
7.2 How will the findings of any safety studies be communicated to the public?
7.3 How will the findings of any safety studies be communicated to other key stakeholders?
7.4 Do the communication plans include how to deal with misinformation and hesitancy regarding vaccine safety?
D.8. Vaccine Uptake
8.1 What is anticipated or is known acceptance of COVID-19 vaccine in the general population?
8.2 What is anticipated or is known acceptance of vaccines by pregnant women?
8.3 What is anticipated or known acceptance of COVID-19 vaccine by pregnant population?
8.4 Will pregnant women choose to participate in clinical vaccine studies?
8.5 Will pregnant women choose to participate in post-licensure vaccine studies?

V.4 SUMMARY OF KEY QUESTIONS

The COVAX MI WG suggests developing a summary of the essential criteria necessary to determine the suitability of

candidate vaccines for pregnant and lactating women and their offspring, based on the responses to the various key questions in Table 1 sections A-D. These are summarized in [Table 1 Section E](#).

Table 1. Section E.

Section E. Summary of Evaluation of COVID-19 Vaccine for use During Pregnancy and Lactation
E.1. Key criteria to suggest/recommend vaccines for:
1.1 Pregnant women
1.2 Lactating women
E.2 Key criteria to reject/not recommend vaccines for:
2.1 Pregnant women
2.2 Lactating women
E.3 Key considerations for proceeding with the evaluation of a vaccine for:
3.1 Pregnant women
3.2 Lactating women
E.4 Safety data needed for inclusion of pregnant/lactating women in clinical studies
E.5 Efficacy data needed for inclusion of pregnant/lactating women in clinical studies
E.6 Development phase(s) in which pregnant/lactating women should be included
E.7 Optimal timing of vaccination during pregnancy
E.8 Communication plan was finalized and accepted by all parties involved
8.1 Has the communication plan been implemented?

VII. MATERNAL IMMUNIZATION WORK GROUP NEXT STEPS

With input from experts, information from the literature, and survey data from a wide range of organizations, specialties, and geographies, the working group members reviewed and opined on all key questions. The COVAX MI WG consensus, along with key responses to the key questions developed by the group, and COVAX MI WG recommendations will be presented in the full COVAX MI WG Project Report. Next steps for the COVAX MI WG are presented in [Table 2](#).

Table 2. Maternal Immunization Working Group Next Steps

COVAX MI WG Next Steps
Share WG findings with a broad spectrum of audiences including vaccine developers; engage pregnant women and antenatal care providers
Systematic literature review on pregnancy exposure data for candidate vaccine platforms and adjuvants, coordinated by Prof. Pierre Buekens in collaboration with the <i>safeinpregnancy</i> advisory board
Update vaccine candidate development timeline mapping (vignettes)
Harmonized methodology to evaluate inadvertent pregnancy exposure data in clinical trials
Conduct ethics review and focused discussion session
Provide summary report on outstanding knowledge gaps/data needs per platform/adjuvant
Develop communication and stakeholder engagement plan

VIII. COVAX MI WG INTERIM REPORT SUMMARY

Over the last several years, significant progress has been made towards the *concept* of including pregnant and lactating women in clinical trials. International regulatory agency guidance documents have been issued on developing vaccines for use during pregnancy and on the inclusion of pregnant women in clinical studies. The actual *practice* of including fully consented pregnant women who want to participate is moving more slowly.

Because pregnant women are considered to be at increased risk for severe COVID-19 disease and potential adverse neonatal outcomes, it is imperative to permit them access and promote their participation in COVID-19 vaccine evaluation. Their inclusion in studies is critical to generate a robust

database pre-licensure, and should continue in the post-licensure environment, to help identify additional vaccine candidates and licensed vaccines that are acceptable for use during pregnancy and lactation. Continued efforts need to be made to characterize the COVID-19-associated disease burden and impact on health outcomes in different geographical settings, particularly those with limited resources.

Optimally, pregnant and lactating women should be included in clinical vaccine trials early in the process of vaccine development to help guide regulatory and policy recommendations at the time of or shortly after licensure. Additionally, post-licensure surveillance studies will be needed in order to characterize the benefit-risk profile in a larger pregnant and lactating women population. In view of the expected additional Emergency Use Approvals (EUAs) for COVID-19 vaccines, additional data sources such as inadvertent exposure to vaccination, as well as vaccine construct- and platform-associated clinical safety data should be identified and evaluated. Continued efforts need to be made to characterize the COVID-19-associated disease burden and impact on health outcomes in different

geographical settings, particularly those with limited resources.

Concerted efforts will be needed to address fears in the public that COVID-19 vaccines may be rushed to market prior to adequate safety evaluation. The Key Questions and responses created by the COVAX MI WG will be a valuable tool for researchers, policy makers, and health care providers to assess the new vaccines' suitability for use by pregnant women.

The COVAX MI WG development of a communication and stakeholder engagement plan to share vaccine evaluation findings broadly will provide the information needed to ensure that pregnant and lactating women have access to COVID-19 vaccines and to assist these women and their health care providers make informed decisions about whether or not to be vaccinated against COVID-19.

APPENDICES

APPENDIX I. Maternal Immunization Working Group Composition

COVAX Maternal Immunization WG Co-chairs: Flor Munoz, Ajoke Sobanjo-ter Meulen					
WS – 1 PRODUCT MAPPING		WS -2 PRE-CLINICAL / CLINICAL		WS -3 VACCINE SAFETY	
Emily <u>Erbelding</u> (LEAD)	Director, Division of Microbiology and Infectious Diseases NIH – ACTIV; US	Beate <u>Kampmann</u> (LEAD)	Professor of Paediatric Infection & Immunity; Director of the Vaccine Centre ; London School of Health and Tropical Medicine; UK	Stephen <u>Anderson</u> (LEAD)	Director, Office of Biostatistics and Epidemiology CBER/WHO-GAVCS; US
Ajoke <u>Sobanjo-ter Meulen</u>	Senior Program Officer, Bill & Melinda Gates Foundation; US	Flor <u>Munoz-Rivas</u>	Associate Professor, Pediatrics-Infectious Disease; Baylor College of Medicine; US	Andrew <u>Stergachis</u> (LEAD)	Professor, Global Health; Professor, Pharmacy Director, Global Medicines Program University of Washington; US
Karin <u>Bok</u>	Senior Advisor Vaccine Development, VRC, NIAID, NIH; US	Geeta <u>Swamy</u>	Associate Professor of Obstetrics and Gynecology, Duke University School of Medicine; US	Steve <u>Black</u>	CEPI-SPEAC; US
Anh <u>Wartel</u>	Associate Director General of Clinical Development, IVI, South Korea	Clare <u>Cutland</u>	Lecturer, University of the <u>Witwatersand</u> ; South Africa	Delese <u>Mimi Darko</u>	Chief Executive Office, Ghana Food and Drugs Authority; Ghana
Angela <u>Gentile</u>	Head, Department of Epidemiology, Ricardo Gutiérrez Children’s Hospital; Argentina	Asma <u>Khalil</u>	Professor, Consultant obstetrician at St George’s Hospital; UK	Christine <u>Guillard-Maure</u>	Global Vaccine Safety Initiative; WHO
Gerald <u>Voss</u>	Scientific Director of the <u>TuBerculosis</u> Vaccine Initiative/ CEPI; Belgium	Helen <u>Marshall</u>	Medical Director VIRTU & A-Prof Vaccinology / Affiliate Lecturer, Women’s and Children’s Health / Public Health; University of Adelaide; Australia	Esperanca <u>Sevene</u>	Associate Professor, <u>Universidade Eduardo Mondlane</u> ; Mozambique
Johan <u>Vekemans</u>	SARS-CoV-2 vaccine Global Clinical Head, AstraZeneca; Belgium	Chrissie <u>Jones</u>	Associate Professor in <u>Paediatric</u> Infectious Diseases and Immunology, University of Southampton; UK		
Titilope <u>Oduyebo</u>	CDC; US ACOG, IIFPHPEWG	Sylvanus <u>Okogbenin</u>	Professor, Consultant Obstetrician, <u>Irrua</u> Specialist Teaching Hospital; Nigeria		
		Judith <u>Absalon</u>	Senior Director ,Vaccines Clinical Research, <u>Pfize</u> ; US		
Cross-cutting advisors					
Marion <u>Gruber</u> (Regulatory)	Director, Center for Biologics Evaluation and Research (CBER) FDA; US	Helen <u>Rees</u> (Regulatory)	Professor, Wits Reproductive Health and HIV Institute, Board Chair SAHPRA; South Africa	Daniel <u>Brasseur</u> (Regulatory)/ CEPI	Former CHMP-PDCO-VWP chair at EMA; CEPI consultant; EU
Ruth <u>Karron</u> (Ethics)	Professor, Johns Hopkins Bloomberg School of Public Health; US	Carleigh <u>Krubiner</u> (Ethics)	Policy Fellow, Center for Global Development, Johns Hopkins Univ; US		

APPENDIX II. COVID-19 Vaccine Candidate Mapping

Product Mapping

Vaccines are those prioritized by COVAX (vaccines funded by COVAX and those in later-stage clinical development)

Vaccine	Platform / Design	Dose / Schedule	Current Status	Phase 3 Est. Start Date	DART	Pregnancy Exposure	Exclusion criteria	Comments
Protein/subunit vaccines								
Novavax	Baculovirus Expressed trimeric Stabilized Spike, ΔF; Matrix M; TM; trimerization domain	2 doses at 5 and 25 μg with/wo Matrix M (0,21 days)	Phase 2/3	Ongoing (UK) To start Fall 2020 (US)	Started last week of Sept. 2020	Baculovirus Expression YES; Adjuvant has been tested in adults		Extensive experience with pregnancy trials (RSV+Alum)
Sanofi/GSK	Baculovirus Expressed trimeric Stabilized Spike, ASO3	5/15 μg + ASO3 (0, 21 days)	Phase 1	TBD	Yes will conduct	Baculovirus expression YES; Adjuvant (ASO3) in commercial vaccine (Pandemrix , Arepanrix)		GSK conducting pregnancy trials (Phase 2) for RSV vaccine
UQ / CSL	Molec clamp S-protein + MF59 (in CHO cells)	2 dose (0,28d)	Phase I	TBD	TBD	No		
Clover	S-protein trimer + /ASO3 /CpG1-18 (in CHO cells)	2 dose (0,21d)	Phase I/II	Oct. 2020	yes	No		
Vectored vaccines								
Merck	rVSV vector full length S-protein (in MRC or Vero cells)	1 dose (TBD)	Preclinical	2021	TBD	YES		
Janssen	Replication Incompetent Ad26; Stab. Spike; ΔF; TM	1 dose at 5E10 vp; 2 doses at 5 x 1010 (0-56)	Phase 1/2/3 international (includes US)	Ongoing	Yes will conduct Mid-study report was good. Draft results by Dec 2020	YES, Ad26 + Ebola (1000 patients); Current pregnancy trials ongoing	Currently recruiting lactating women in all Phase 3	
U Oxford / AstraZeneca	Replication incompetent ChAdOx1 wild type Spike; ΔF; TM	2 doses at 5 x 1010 vp, (0-28 days)	Phase 3 International	Phase 3 currently on hold in US	Yes will conduct	No; Platform has been tested in adults		Two reports of transverse myelitis
Nucleic acid/mRNA vaccines								
Moderna	mRNA: encodes 2P-stabilized Spike, TM, FI	2 doses at 100 μg (0,28 days)	Phase 3 US (start date July 27th)	Ongoing	Yes will conduct Draft report by December 2020	No; Platform has been tested in adults		
Biontech / Pfizer	mRNA: encodes stabilized SARS-CoV-2 Spike	2 doses X 30 μg (0, 21 days)	Phase 2-3 International (start date July 27th)	Ongoing	Yes will conduct	No		Pfizer Experience with RSV and GBS studies in pregnancy
Curevac	mRNA/LNP full length S-protein stabilized	2 dose (0,28d)	Phase I	Nov. 2020	yes	No, Platform has been tested in adults		
Live vaccines								
Hong Kong U	LAIV (delNS1-nCoV-RBD) grown in eggs	1 or 2 dose (TBD)	Preclinical	TBD	TBD	No		Live not considered an option

APPENDIX III. Key Characteristics for Maternal Vaccines for COVID-19 WHO Target Product Profiles (TPP) Annex

Variable	Minimum <i>The minimal target should be considered as a potential go/no go decision point.</i>	Optimistic <i>The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact.</i>	Annotations
Indication	<ul style="list-style-type: none"> Prevention of severe COVID-19 disease in adults Safe and immunogenic in pregnant and lactating women 		<ul style="list-style-type: none"> Reduction of hospitalization Reduction of ICU admissions Reduction of mechanical ventilation Reduction of pre-term births What is the disease burden in infants? Not known at this time
Target Population	<ul style="list-style-type: none"> Pregnant women 24-36 weeks gestation Lactating women 	<ul style="list-style-type: none"> Pregnant women, any gestational age Lactating women 	
Maternal Safety	<ul style="list-style-type: none"> No evidence of adverse pregnancy outcomes No evidence of severe side effects Transient and mild-moderate local reactions 		<ul style="list-style-type: none"> Safety in lactating women? Breastmilk transmission?
Infant Safety	<ul style="list-style-type: none"> No evidence of adverse birth outcomes No enhanced disease in first 6 months of life 		<ul style="list-style-type: none"> Omitted: “No evidence of clinically significant impact on infant immunizations” as will be extremely difficult to prove
Efficacy	<ul style="list-style-type: none"> 50% of PCR-confirmed COVID-19 disease in pregnant women 	<ul style="list-style-type: none"> 70% of PCR-confirmed COVID-19 disease in pregnant women 	<ul style="list-style-type: none"> Reduction in hospitalization, mechanical ventilation
Immunogenicity	<ul style="list-style-type: none"> Achieve durable NT Ab in the mother exceeding identified biomarker 	<ul style="list-style-type: none"> Achieve transplacental transfer of maternal NT Ab to the infant exceeding identified biomarker 	
Dose Regimen	<ul style="list-style-type: none"> <u>Non-pandemic</u>: 1 dose prior to pregnancy, booster at 24-36 <u>wks</u> gestation <u>Pandemic</u>: Single dose 24-36 <u>wks</u> gestation, booster post-partum 		<ul style="list-style-type: none"> If two doses are needed for full protection in non-pregnant adults, do we propose to give 2 doses during pregnancy for pandemic scenario?

Appendix III. cont. Key Characteristics for Maternal Vaccines for COVID-19 WHO Target Product Profiles (TPP) Annex

Variable	Minimum <i>The minimal target should be considered as a potential go/no go decision point.</i>	Optimistic <i>The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact.</i>	Annotations
Durability of protection	<ul style="list-style-type: none"> Mother: 6 months 	<ul style="list-style-type: none"> Mother: 1 year Infant: 3 months 	<ul style="list-style-type: none"> Single pregnancy vs. every pregnancy?
Route of administration	<ul style="list-style-type: none"> Vaccine construct dependent 		
Product	<ul style="list-style-type: none"> Subunit, non-live vaccine, non-replicating 	<ul style="list-style-type: none"> May include novel adjuvant 	
Product Stability & Storage	<ul style="list-style-type: none"> Minimum shelf life of 2 years at 2-8 C Vaccine vial monitor (VVM)-7 If freeze sensitive, use of cryoprotection formulation or allow use of shake test or include other indicator of freezing 	<ul style="list-style-type: none"> Minimum shelf life 3 years at 2-8 C Vaccine vial monitor (VVM)-30 Not freeze-sensitive Use of vaccine for a minimum period of 2 months when stored at a controlled temperature chain at temperatures up to 40 C 	
Co-administration with other vaccines	<ul style="list-style-type: none"> Can be administered with other routinely administered maternal vaccines (DT, Tdap, Influenza) No evidence of clinically significant impact on infant immunizations 		
Presentation	<ul style="list-style-type: none"> Single-dose vial, liquid formulation 	<ul style="list-style-type: none"> Both single-dose and multi-dose (no-thimerosal preservative) vial, liquid formulation 	
EUA/WHO EUL Registration and PQ	<ul style="list-style-type: none"> Outbreak: WHO prequalified and or made available under EUA/WHO EUL LT: WHO prequalified 		
Accessibility	<ul style="list-style-type: none"> Outbreak: Capability to rapidly scale-up production at cost/dose that allows broad use, including in LMIC LT: Availability of sufficient doses at cost/dose that allows broad use, including in LMIC 		

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