COVAX Maternal Immunization Working Group

PROJECT REPORT

Considerations for the evaluation of COVID-19 vaccines in pregnant and lactating women

February 2021

COVAX

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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
AEFI – Adverse Event Following Immunization
AESI – Adverse Event of Special Interest
BLA – Biological License Application
BMGF – Bill and Melinda Gates Foundation
CDC – U.S. Centers for Disease Control and Prevention
CEPI – Coalition for Epidemic Preparedness Innovations
CIOMS - Council for International Organizations of Medical Sciences
COVAX – COVID vaccine arm of the Access to COVID-19 Tools Accelerator
CoVPN – COVID-19 Prevention Network
DART – Developmental and Reproductive Toxicology
EUA – Emergency Use Authorization (FDA)
FDA - U.S. Food and Drug Administration
GAVI – Global Alliance for Vaccines and Immunizations
HIC – High Income Country
ICU – Intensive Care Unit
IDCRC – Infectious Diseases Clinical Research Consortium
IgA, IgG, IgM – Immunoglobulin antibody types
IMPRINT - Immunizing Pregnant Women and Infants Network
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
MIWG – Maternal Immunization Working Group
mRNA – Messenger RNA
NAM - U.S. National Academy of Medicine
OWS – Operation Warp Speed
PPE – Personal protective equipment
PREVENT - Pregnancy Research Ethics for Vaccines, Epidemics, and new Technologies
PVP – Pharmacovigilance Plan
SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2; COVID-19 virus
TPP - Target Product Profiles
UN – United Nations
WG – Working Group
WHO - World Health Organization

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 health care global workforce. Among the health care workforce in the United States (U.S.) there are over 300,000 women who are of child-bearing age and/or 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 is 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 FDA and Advisory Committee on Immunization Practices (ACIP) review of data submitted for Emergency Use Authorization (EUA). 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 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 [see Table 1]. 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 on pregnancy outcomes associated with COVID-19 is available from LMICs largely due to a lack of data collection infrastructure. 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 vaccines currently approved for emergency use. According to several reports, "clinical studies in pregnant women are planned"[29,30] and two studies have

recently commenced or will begin shortly.[31,32] Data from animal studies are anticipated to become available shortly and, according to the American College of Obstetricians and Gynecologists (ACOG), "there have not been any major safety signals identified."[33]

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.[34,35] Various organizations, including the U.S. National Academy of Medicine (NAM),[36] the American College of Obstetrics and Gynecology (ACOG),[37] the Pregnancy Research Ethics for Vaccines, Epidemics, and new Technologies (PREVENT) group,[38] the Society for Maternal-Fetal Medicine,[39] and the World Health Organization (WHO)[40] support the position that pregnant and lactating women are a priority population that must not be excluded from the COVID-19 vaccine allocation strategy.[41,42]

On December 12, 2020, guidelines for the immunization of pregnant and lactating women were included in the CDC COVID-19 vaccine allocation guidance[43] which can be summarized as follows:

There are no safety or efficacy data available from clinical experience with pregnant or lactating 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.
- 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 WHO, 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."[44] [see Table 1. Current guidance]

Table 1. Current guidance regarding COVID-19 vaccines in pregnancy

Organization	Recommendations
WHO	SAGE Meeting Dec 17th ,2020 - pregnant or lactating women **should not be vaccinated** with COVID-19 vaccines **unless** they are in high risk group. Language modified in January 2021 to indicate that **pregnant and lactating women at risk may be vaccinated if at high risk of exposure (health care workers).**
UK MHRA	"There are no data as yet on the safety of COVID-19 vaccines in pregnancy, either from human or animal studies. Given the lack of evidence, JCVI favours a precautionary approach, and d**oes not currently advise COVID-19 vaccination in pregnancy.** Women should be advised not to come forward for vaccination if they may be **pregnant or are planning a pregnancy** within three months of the first dose. **Language then changed (Dec 30th, 2020) to be in line with ACIP recommendations**
US FDA	"If you are **pregnant or breastfeeding**, **discuss your options** with your healthcare provider." No specific contraindications to vaccination other than anaphylaxis/allergic reactions.
US CDC-ACIP	"If the **pregnant or lactating woman** is part of a priority group (i.e. healthcare personnel) who is recommended to receive a COVID-19 vaccine and is pregnant, **she may choose to be vaccinated**. A discussion with her healthcare provider can help her make an informed decision."
US ACOG/SMFM	"COVID-19 vaccines **should not be withheld** from pregnant individuals who meet criteria for vaccination based on ACIP-recommended priority groups." **Shared decision making** with clinicians is advisable; however, it should not be required as this may create an undue barrier to access for these women. Breastfeeding women can get vaccinated.

-Flor Munoz, MIWG/COVAX webinar 16 Dec 2020 (updated)

II. THE MATERNAL IMMUNIZATION WORKING GROUP

In April 2020, in response to the COVID-19 pandemic, the Access to COVID-19 Tools (ACT) Accelerator[45], 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 SWOT team to identify product-agnostic 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 (MIWG) in August 2020.

The COVAX MIWG, co-chaired by Drs. Flor M. Munoz (Baylor College of Medicine) and Ajoke Sobanjo-ter Meulen (Bill & Melinda Gates Foundation) invited a selected 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 MIWG is comprised of members from various disciplines including academia, regulatory, medicine, ethics, clinical research, industry, pharmacovigilance, and vaccine safety [MIWG Composition, Appendix I]. Members of the MIWG are contributing at many levels including via relevant maternal immunization projects such as WHO's multi-country study on maternal immunization safety surveillance,[46] IVAC/JHPIEGO's project on COVID-19 maternal immunization implementation preparedness,[47] the National Institutes of Health (NIH) Operation Warp Speed,[48] Infectious Diseases Clinical Research Consortium (IDCRC),[49] Immunizing Pregnant Women and Infants Network (IMPRINT),[50] and industry efforts to advance maternal vaccines through clinical development.

The aim of the COVAX Maternal Immunization Working Group (COVAX MIWG) 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.

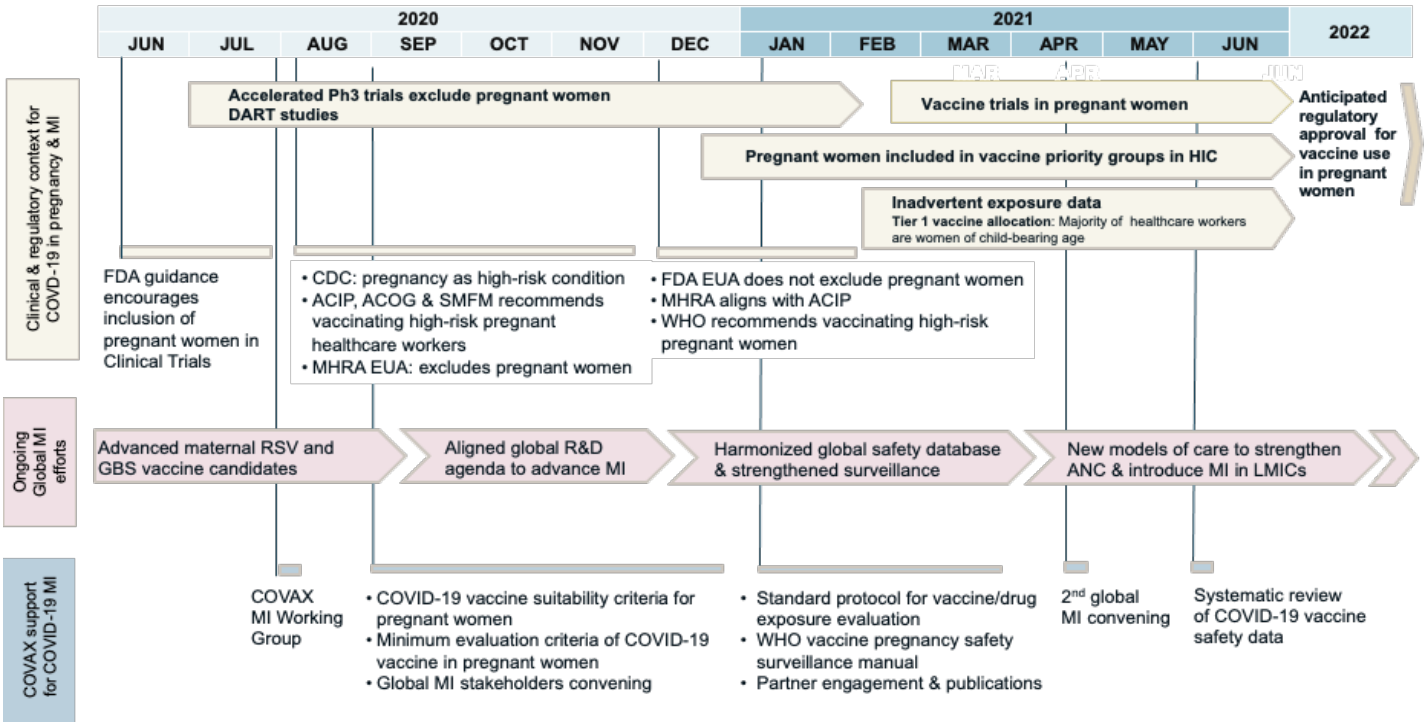
III. SCOPE OF WORK

The COVAX MIWG's scope of work consists of 1) the identification of research and development needs towards COVID-19 vaccine recommendations for pregnant and lactating women, and 2) contribution to the alignment of the tasks and objectives of the COVAX MIWG with global efforts towards the evaluation and implementation of COVID-19 vaccines for maternal immunization.

IV. PROJECT OBJECTIVES

The overarching goal of the COVAX MIWG is to support the availability of at least one COVID-19 vaccine candidate that is suitable for use by pregnant and lactating women. To accomplish this goal, the MIWG set out to 1) describe approaches for the evaluation of COVID-19 vaccine candidates for use in pregnant and lactating 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. [Figure 1 shows the timeline of vaccine development through the COVID-19 crisis.]

Figure 1. Accelerating the Inclusion of Pregnant Women in COVID19 Vaccine Development Efforts



V. APPROACH

In order to cover relevant issues pertaining to the inclusion of pregnant and lactating 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, as shown in Table 2, related to:

1) Vaccine Candidate Mapping,

2) Pre-clinical and Clinical Evaluation, and

3) Vaccine Safety

On an ad hoc basis, workstream leads and members also solicited input from external subject matter experts. The Working Group's ethics and regulatory members 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.

Table 2. Workstream Responsibilities and Methods

Workstream 1. Vaccine Candidate Mapping / Key Characteristics – Lead: Dr. Emily Erbelding, US NIH
▪ 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
▪ 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 MIWG 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
▪ Identification of pregnancy safety considerations for four vaccine development scenarios: o Pregnant and lactating women not included in pre-licensure clinical trials, i.e., excluded from clinical trials. o Pregnant and lactating women included in pre-licensure clinical trials. o Separate pre- (or post-) licensure clinical trial specifically designed for pregnant and lactating women. o Post-licensure safety surveillance ▪ Review and consideration of key regulatory and WHO guidance documents pertaining to pregnancy and lactation 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"[51] (Lead: Prof. Pierre Buekens, Tulane University)," with collection and evaluation of written responses.
Cross-cutting Workstreams
Review and input from ethics and regulatory experts across all work streams

VI. OUTPUTS

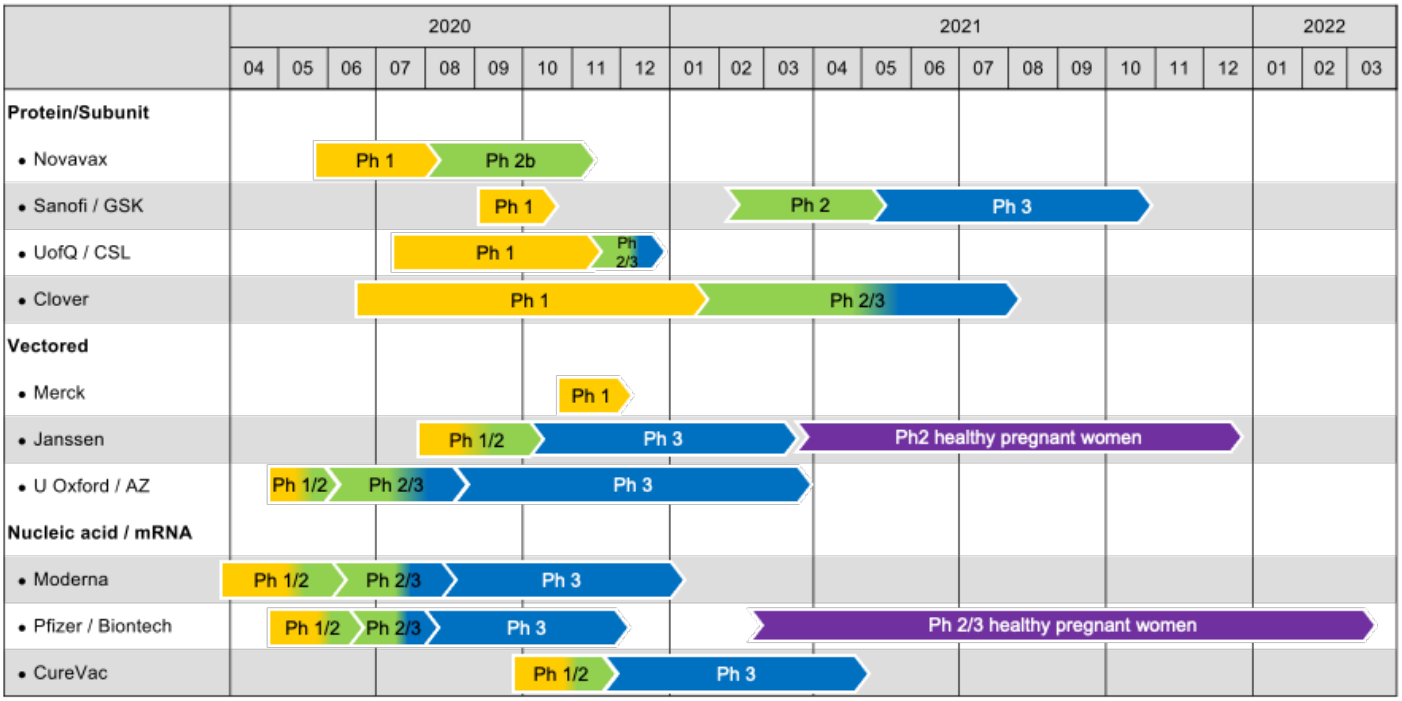
VI.1 VACCINE CANDIDATE MAPPING, KEY CHARACTERISTICS, AND DEVELOPMENT TIMELINE

The MIWG developed a dynamic, candidate-specific, product map indicating key components, clinical development status, timeline to approval and other characteristics relevant to their potential use in pregnant and lactating women. These eleven COVID-19 vaccine candidates prioritized by COVAX and their stages of development are shown in Appendix II.

VI.1.1 Vaccine development details at a glance

The vaccine candidate vignettes developed by the MIWG present a visualization of the vaccine candidate's progress along the clinical development path. At the same time, they allow an estimation of the potential timing of including pregnant and lactating women in the development path. These vignettes can be updated as additional information becomes available and are supplemented by the MIWG's evaluation and identification of additional data and studies that are needed to close the gap between approval and administration to pregnant and lactating women

FIGURE 2. Projected availability of COVID-19 vaccines prioritized by COVAX - estimated timelines and availability for pregnant women (based on public existing and planned studies)



VI.1.2. Key Characteristics for Maternal Vaccines Annex

WHO formulated a Target Product Profile[52] (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, the MIWG identified the key characteristics of vaccines against COVID-19 that would make them acceptable for use by pregnant or lactating women. As a complementary annex to the WHO TPP, these key characteristics for a maternal vaccine likewise focus on minimum and optimistic variables for pregnant and lactating women [see Key Characteristics for Maternal Vaccines for COVID-19 TPP, Appendix III].

VI.2. CRITERIA FOR THE EVALUATION OF COVID-19 VACCINE CANDIDATES FOR USE BY PREGNANT AND LACTATING WOMEN

The MIWG aimed to develop a set of criteria necessary for the evaluation of candidate COVID-19 vaccines in pregnant and lactating women and provide guidance to COVAX, vaccine developers and stakeholders. Three specific objectives were identified and are discussed below.

Objective 1: Identify COVID-19 vaccine pre-clinical and clinical development needs and timing for evaluation in pregnant and lactating women in the context of overall COVID-19 vaccine development.

At the current time, there is no clear evidence of placental infection, or vertical transmission of SARS-CoV-2 to infants, either in utero or at the time of delivery, although there are case reports.[53,54] Infants who are born to mothers with COVID-19 generally have good outcomes and only rarely has neonatal SARS-CoV-2 infection been proven following maternal infection. Recent studies are indicating the vertical transmission of IgG antibodies in concentrations correlated with maternal antibody concentration and duration of time between onset of infection and time of delivery.[55,56]

Given the current evidence, there is consensus from the MIWG that the pregnant or lactating woman is the primary target for immunization, rather than the fetus/newborn.

However, in clinical trials or post-licensure studies, data should be collected regarding the potential for infant protection following vaccination of the mother during pregnancy, including transplacental transfer of SARS-CoV-2 specific immunoglobulin G (IgG), the half-life of maternal SARS-CoV-2 specific IgG in the infant during the first six months of life, and infant health and developmental outcomes to assess safety of the infant following vaccination of the mother during pregnancy. In addition, antibodies levels in breastmilk and transferred antibody levels in breastfed infants should be measured along with infant developmental milestones to assess infant safety.

Prevention of severe disease from SARS-CoV-2 infection in the mother is the principle aim of vaccination in pregnancy. Data on effectiveness of a vaccine against severe disease and outcomes such as hospitalization and mortality will need to be collected post-licensure for all recipients, but especially for pregnant women due to their exclusion from clinical trials.

The MIWG has concluded that separate efficacy trials in pregnant and lactating women are not required because a) there is no reason to believe that a vaccine that has been found to be efficacious in the general population should not also protect pregnant and lactating women and b) we are not aiming for licensure of a vaccine with indication specifically in pregnancy or lactation but the aim is a general license that would not exclude pregnant or lactating women.

Objective 2: Provide criteria to address the identified needs to evaluate COVID-19 vaccines in pregnancy.

The MIWG agreed that as a minimum, preclinical data from DART studies and data from clinical trials in non-pregnant adults demonstrating safety and immunogenicity should be established prior to enrolment of pregnant women in COVID-19 vaccine trials with any of the candidate vaccines.

Considerations of the suitability of a vaccine construct or platform for use in pregnancy can be based on the evaluation of the criteria in Table 3.

Table 3. Criteria to Evaluate COVID-19 Vaccines for Use in Pregnant Women

Criteria to Evaluate COVID-19 Vaccines for Use in Pregnant and Lactating Women
1 Prior knowledge of the antigen and delivery system (subunit, non-replicating vector, vectored, mRNA, DNA, etc.) in pregnant and lactating populations
2 Results of developmental and reproductive toxicity (DART) studies, with advice to developers to plan for expeditious conduct, analysis, and release of DART data
3 The safety data available from use of the same vaccine platform in non-pregnant populations
4 The safety data available from use of the same vaccine candidate in non-pregnant populations
5 If the adjuvant-antigen pair has been tested in non-pregnant adults, as long as there is data from DART studies for the adjuvanted construct
6 Safety data from clinical trials in pregnant and lactating women of vaccines utilizing the same adjuvant and/or the same platform as the candidate COVID-19 vaccine
7 Safety data from participants in clinical trials of a COVID-19 vaccine who have become pregnant whilst in the trial
8 Data on fever from clinical trials of the candidate vaccine in non-pregnant populations as an indication of the potential for fever post vaccination in pregnant women.
9 The local and systemic reactogenicity profile of the candidate vaccine in non-pregnant population as an indication of the possible local and systemic reactogenicity profile in pregnant women
10 Data from post-licensure studies and vaccine registries when planning post-licensure studies in pregnant and lactating women
11 Follow up for safety: The MIWG recommends a minimum 6-month follow-up period for infant safety evaluation; a 12-month period is preferred

The MIWG determined that all studies that include pregnant or lactating women should collect efficacy outcome data, even if not powered for this outcome. Adverse outcomes following vaccination of pregnant or lactating women should be designated as adverse events of specific interest (AESI) and should be a secondary objective within a phase 2/3 study in pregnant and lactating women, particularly if efficacy data from phase 3 trials in non-pregnant adults is available.

The potential maternal and obstetric consequences of vaccination should be considered, as the risk of vaccine-associated enhanced disease may be higher, given pregnancy is associated with Th2 weighted responses, but may also be lower as pregnancy is also associated with lower pro-inflammatory responses. The follow-up period for maternal and infant participants should be considered in order to ensure vaccine-associated enhanced disease can be captured. The clinical development plan should include the means and metrics to identify and evaluate enhanced disease (clinical and laboratory means), vs. the usual reactogenicity/ tolerability and safety.

Priority should therefore be given to bridging studies, with safety and immunogenicity of a COVID-19 vaccine in pregnancy compared with non-pregnant populations. This could be done in a phase 2 study or a phase 2/3 study where efficacy outcomes are also collected, even if the study is not powered for efficacy outcomes in pregnancy per se.

A COVID-19 vaccine that has been demonstrated to be safe and immunogenic in non-pregnant adults could be evaluated in Phase 2/3 studies for:

- **safety** in pregnant women
- **immunogenicity** in pregnant women
- **efficacy** against severe disease in pregnant women

Safety/immunogenicity studies in pregnant women should be conducted after efficacy is confirmed in adult non-pregnancy phase 3 studies in vaccines that have reached this phase of development. Placebo studies have ethical issues, consider an unblinded comparison between pregnant women who have consented to the vaccine and pregnant women who have declined the vaccine but agreed to participate in a follow-up study.

Preclinical	DART study results are necessary for vaccines that will be administered to pregnant women
Phase 1	Pregnant women should be excluded due to very narrow safety data collection and unknown immunogenicity
Phase 2	Pregnant women could be considered for inclusion if safety data are available in pregnant women from vaccines using a similar platform, and/or safety and immunogenicity has already been established in studies conducted in non-pregnant adult populations
Phase 3	Ideal phase for inclusion of pregnant women during a pandemic, and when they represent a high-risk group they should be considered for inclusion as a subgroup in efficacy trials, with an appropriate follow-up of the pregnancy, mother, and infant for at least six months post-vaccination
Phase 4	Pregnant women should be monitored, including evaluation of secondary outcomes such as prevention of pregnancy complications. Clinical trials may be conducted in Phase 4 specifically for pregnant women

Objective 3: Provide criteria to address the identified needs to evaluate SARS-CoV-2 vaccines in lactating women

Given that there is currently no evidence of direct viral transmission via breastmilk of either COVID-19 or any of the vaccine vectors used in viral platforms, the MIWG concluded that lactating women should not be excluded from any COVID-19 vaccine trials unless DART study data had raised concerns. Vaccine-induced antibodies in breast milk should be measured as part of ongoing trials.

VI.3 KEY QUESTIONS FOR THE EVALUATION OF COVID-19 VACCINE CANDIDATES FOR PREGNANT AND LACTATING WOMEN (BRIGHTON COLLABORATION)

Key questions for the evaluation of any COVID-19 vaccine's potential for use during pregnancy and lactation were developed by the MIWG and are shown in Appendix IV. These key questions for the assessment of the suitability of vaccine candidates for administration to pregnant and lactating women will support COVAX's goal of identifying vaccines that are appropriate for use by pregnant and lactating women.

The table of key questions serves 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 by pregnant or lactating women:

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

Section B. General 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

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

Upon finalization of the list of key questions to be applied to COVID-19 vaccine candidates, the MIWG co-chairs approached the Brighton Collaboration to discuss the efficiency that might be gained by transforming the key questions table into a Brighton Collaboration template. The Brighton Collaboration BRAVATO[57] project created templates to aid in the identification and assessment of the characteristics of specific vaccine platforms used by the non-pregnant population.[58,59,60,61,62] When pertinent, data collected through Brighton Collaboration tools can be complimented by the MIWG Key Questions for the evaluation of vaccine candidates intended for use by women of childbearing potential and/or for use by pregnant and

lactating women, not necessarily limited to COVID-19 vaccine candidates.

VI.3.1. The safety evaluation of COVID-19 vaccines in the post-licensure environment

Safety evaluation of pharmaceuticals, including vaccines, continues throughout the market lifetime of a product. Since pregnant and lactating women are actively excluded from most clinical trials, a sufficient level of pregnancy safety information is rarely available at the time of product licensure. The small number of women who experience inadvertent pregnancies during a pre-licensure clinical trial, are followed to pregnancy outcome by the clinical monitors. Their infants, who experienced medical product exposure in utero, may be followed up at intervals, ideally for at least the first year of life.

FDA and analogous authorities recommend that, prior to enrolling pregnant women and women of childbearing potential who are not actively avoiding pregnancy in clinical trials, sponsors complete developmental and reproductive toxicity (DART) studies with their respective COVID-19 vaccine candidate. Alternatively, sponsors may submit available data from DART studies with a similar product using comparable platform technology if, after consultation with the agency, the agency agrees those data are scientifically sufficient.

Various methods are employed to routinely collect and evaluate reports of adverse events following immunization (AEFIs) and additional surveillance activities may be mandated as a condition of license or emergency use authorization (EUA) approval by regulatory agencies. As medical products are used in large numbers by the general public under real-world conditions, important data about unexpected or rare events becomes available for evaluation. Rates and risk factors of AEFIs can be calculated from active surveillance. The information can then be shared with health care providers and the general population primarily via the drug labels and other means of communication. Post-licensure or post-EUA safety surveillance during pregnancy should include:

- Routine, passive, pharmacovigilance includes the voluntary reporting of adverse events following immunization by health care providers and the public. Pharmaceutical companies are compelled to collect, analyze, and forward reports of serious adverse events at regular intervals to regulatory agencies that also collect and monitor voluntary reports.
- Because of the lack of pregnancy exposure data collected during development, more active surveillance methods are commonly required post-licensure by regulatory agencies for products intended for use by women of childbearing potential. Active methods are an important adjunct to routine surveillance, in part, because their prospective design allows for the collection of detailed patient-level data prior to outcome, thereby decreasing bias.
    - Pregnancy registries collect exposure and outcome data from pregnant and lactating women or health care providers using various outreach methods to encourage reporting, e.g., notice of a pregnancy registry and its phone number are included in the pregnancy section of a product label.
    - Phase 4 studies are another active surveillance tool for safety data collection in the post-licensure setting. They can be designed to focus on specific populations or subgroups or concomitant medical conditions or medications.

At the time an application for regulatory agency approval of a new vaccine is submitted, the vaccine developer is required to submit a pharmacovigilance plan identifying populations that have not been studied or have only been studied to a limited degree. The plan must include a discussion of the implications of their exclusion on the company's ability to predict the safety of the product in the marketplace and the activities they plan to initiate to improve their understanding of the benefit-risk profile post-approval.[63]

According to FDA guidance in the U.S.,[64] "the plan should include actions designed to address all important identified risks, important potential risks or important missing information." Pharmacoepidemiologic studies or other actions to evaluate notable potential risks should be considered. FDA and other regulatory agencies may recommend one or more of the practical components of a pharmacovigilance plan for a COVID-19 vaccine shown in Table 4.

All methods of vaccine safety assessment need to be conducted in a harmonized and standardized manner so that data are comparable across different trials and populations.

Table 4. Recommended Components of a Pharmacovigilance Plan

Recommended Components of a Pharmacovigilance Plan
1 Submission of reports of specific adverse events of special interest in an expedited manner beyond routine required reporting;
2 Submission of adverse event report summaries at more frequent intervals than specified for routine required reporting;
3 Ongoing and/or extended safety follow-up for vaccine-associated illness in subjects enrolled in pre-licensure clinical studies;
4 A pharmacoepidemiologic study to further evaluate (an) important identified or potential risk(s) from the clinical development program, such as vaccine-associated illness or other uncommon or delayed-onset adverse events of special interest;
5 A pregnancy exposure registry that actively collects information on vaccination during pregnancy and associated pregnancy and infant outcomes.

VI.4. STAKEHOLDER WEBINAR

On December 16, 2020, COVAX, supported by the Coalition for Epidemic Preparedness Innovations (CEPI), the Global Alliance for Vaccines and Immunizations (GAVI), and WHO, hosted a webinar organized by the COVAX MIWG entitled **"Accelerating Access to COVID-19 Vaccine for Pregnant and Lactating Women – What do Developers Need to Know?"** The goal of the webinar was to bring together maternal immunization experts and vaccine developers to discuss the key considerations for facilitating access to COVID-19 vaccines for pregnant and lactating women. Over 300 people attended the webinar representing over 150 institutions including drug developers, funders, regulators, universities and research centers. See Consensus Statements in Table 5. (A detailed report from the webinar can be found here: https://epi.tghn.org/covax-overview/clinical/maternal-immunization/#ref1)

The webinar chairs, Dr. Melanie Saville (CEPI) and Dr. Ajoke Sobanjo-ter Meulen (BMGF), provided background on the status of COVID-19 vaccine research as of December 2020. As pregnant and lactating women remain excluded from current Phase 3 trials, vaccine exposure and outcome data in this population are limited to what is available from those who inadvertently became pregnant and received the vaccine during their enrollment in clinical trials. Emergency use authorizations (EUA) for COVID-19 vaccines differ by country, with vaccination of pregnant and lactating women permitted under the US EUA, but at the time of this event, not yet recommended in the UK.
(UK recommendations were updated since the webinar took place. The guidance for healthcare providers states that animal studies do not indicate direct or indirect harmful effects in pregnancy, embryo/fetal development, parturition or post-natal development, and that administration of the vaccine in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.)[65]

Table 5. Consensus Statements from 'Developers Need to Know' Webinar

Consensus Statements from 'Developers Need to Know' Webinar
Pregnant women • Pregnant healthcare workers or those of childbearing age should be given the option to receive COVID-19 vaccination and that hypothetical concerns should not be barriers if they are not biologically plausible or when there is no evidence for harm while there is potential for benefit • Pregnant healthcare workers have been the main population discussed but other pregnant frontline workers (e.g. custodians, bus drivers, etc.) may have higher risk of exposure to COVID-19 as they do not have access to personal protective equipment (PPE) and should also be considered from a risk/benefit prospective • Programmatic guidance covering complex issues from family planning to pregnancy outcomes is needed • Robust safety monitoring is key. WHO and COVAX are working on developing a pregnancy module for COVID-19 vaccine safety surveillance.
Lactating women • There should be a distinction between pregnant and lactating women and advice may differ between the two groups • Lactating women should have access to COVID-19 immunization as do other members of the non-pregnant adult population
Communications • Need for effective communication to give confidence and allow pregnant and lactating women to make informed decisions based on the available evidence • Lessons learnt on communication of vaccine safety to the media/public should be considered as coincidental events can be very damaging to public confidence in vaccines, especially in pregnant women • During this pandemic, we are having to communicate to a group of people who wouldn't normally receive vaccines and rumors are already widespread. Engagement of healthcare providers such as obstetricians and midwives is key to help reduce vaccine hesitancy in pregnant and lactating women and to manage expectations regarding AEFIs • Stakeholders vary culturally, with family very much involved in decisions for pregnant and lactating women in some cultures.

The webinar concluded with a panel discussion highlighting the need for high quality data on COVID-19 vaccination in pregnant and lactating women going forward. Drs Sobanjo-ter Meulen and Seville's key take-aways from the webinar are summarized in Table 6.[66]

Table 6. Four Key Take-Aways from 'Developers Need to Know' Webinar

Four Key Take-Aways from 'Developers Need to Know' Webinar
• Collaborative effort and co-ordination between stakeholders is essential
• Priority need for high quality data at all levels, with harmonized protocols and data collection tools for assessing outcomes
• Risk vs benefit should be assessed at both population and individual levels
• Continued education and clear communication programs are key to maintaining confidence

VII. MATERNAL IMMUNIZATION WORK GROUP NEXT STEPS

With input from experts within and outside of the MIWG, information from the literature, and workshop and survey data from a wide range of organizations, specialties, and geographies, the MIWG consensus is that pregnant and lactating women need and deserve the collection and review of high-quality, standardized data, the opportunity to consent to participate in ongoing efforts to collect that data via regulated clinical studies, and the benefits of maternal immunization to protect them and their infants from COVID-19 infection. Next steps for the MIWG are presented in Table 7.

Table 7. Maternal Immunization Working Group Next Steps

Maternal Immunization Working Group Next Steps
• Optimize communications and stakeholder engagement plans
• Monitor and support pregnancy exposure data collection and safety surveillance efforts for WHO and other stakeholders
• Maintain vaccine candidate development timelines and availability to pregnant and lactating women
• Support harmonizing methodologies across vaccine development and evaluation efforts
• Review ethical practices and regulatory updates in the maternal immunization environment
• Monitor development of COVID-19 vaccine candidates and licensed products intended for use by pregnant and lactating women
• Conduct ongoing stakeholder webinars

VIII.COVAX MIWG PROJECT REPORT SUMMARY

The COVAX Maternal Immunization Working Group supports inclusion of pregnant and lactating women in COVID-19 vaccine development and implementation efforts and the development of various maternal immunization modules aimed at providing harmonized guidance, data collection tools, and causality assessments for the evaluation of vaccine safety in pregnant and lactating women.

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 or lactating women in clinical studies. The actual practice of including fully consented pregnant or lactating 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 to 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 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 developed by the MIWG are currently being converted into a Brighton Collaboration standardized template for the collection of key information for the benefit-risk assessment of vaccines for pregnant and lactating women. The template will be a valuable tool for researchers, policy makers, and health care providers to assess the new vaccines' suitability for use by pregnant and lactating women.

Introduction of new vaccines requires careful and appropriate risk communication planning. Maternal immunization has heightened sensitivities that could lead to perceived safety concerns. Advanced communication planning is essential for disseminating safety findings to key stakeholders, including patients, the public, health care professionals, national ministries of health (e.g., public health programs, pharmacovigilance centers). Risk communication, when done correctly, can strengthen credibility and maintain trust in immunization

APPENDICES

APPENDIX I: COVAX Maternal Immunization Working Group Members

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 Erbelding (LEAD) Basic, translational and clinical Infectious disease and AIDS research	Director, Division of Microbiology and Infectious Diseases NIH/NIAID; US	**Beate Kampmann (LEAD)** Immunology, Vaccines, MI, clinical trials, epidemiology, research in LMIC	Professor of Paediatric Infection & Immunity; Director of the Vaccine Centre ; London School of Health and Tropical Medicine; UK	**Stephen Anderson (LEAD)** Statistics of vaccine safety and evaluation, Regulatory, MI	Director, Office of Biostatistics and Epidemiology CBER/WHO-GAVCS; US
Ajoke Sobanjo-ter Meulen MI Clinical vaccine development	Senior Program Officer, Bill & Melinda Gates Foundation; US	**Flor Munoz-Rivas** MI clinical trials, Vaccine safety, GAIA case definitions	Associate Professor, Pediatrics-Infectious Disease; Baylor College of Medicine; US	**Andy Stergachis (LEAD)** MI pharmacovigilance, vaccine safety, pregnancy registries	Professor, Global Health; Professor, Pharmacy Director, Global Medicines Program University of Washington; US
Karin Bok Vaccines, research development, policy	Senior Advisor Vaccine Development, VRC, NIAID, NIH; US	**Geeta Swamy** ACOG, NVAC and VRBPAC member, OB clinician	Associate Professor of Obstetrics and Gynecology, Duke University School of Medicine; US	**Steve Black** Vaccine safety, safety surveillance	CEPI-SPEAC; US
Anh Wartel Vaccine development, epidemiology, South East Asia	Associate Director General of Clinical Development, IVI, South Korea	**Clare Cutland** MI Vaccine clinical trials, implementation	Lecturer, University of the Witwatersand; South Africa		
Angela Gentile Pediatric infectious diseases and maternal immunization research in LAM, policy	Head, Department of Epidemiology, Ricardo Gutiérrez Children's Hospital; Argentina	**Asma Khalil** Obstetrician, maternal-fetal medicine, vaccine studies, MI, RCOG member	Professor, Consultant obstetrician at St George's Hospital, UK	**Delese Mimi Darko**	Chief Executive Office, Ghana Food and Drugs Authority; Ghana
Gerald Voss Vaccine development	Scientific Director of the Tuberculosis Vaccine Initiative/ CEPI; Belgium	**Helen Marshall** Vaccines, MI, clinical trials, epidemiology, implementation, regulatory	Medical Director VIRTU & A-Prof Vaccinology Affiliate Lecturer, Women's and Children's Health / Public Health; University of Adelaide; Australia	**Christine Guillard** Clinical trials, Vaccine safety, Pregnancy surveillance	Global Vaccine Safety Initiative; WHO
Johan Vekemans Maternal Immunization	SARS-CoV-2 vaccine Global Clinical Head, AstraZeneca; Belgium	**Christine Jones** Vaccines, MI, clinical trials, infectious diseases	Associate Professor in Paediatric Infectious Diseases and Immunology, University of Southampton; UK	**Esperanca Sevene** PV, Epidemiology and vaccine research in LMIC, Pregnancy registries	Associate Professor, Universidade Eduardo Mondlane, Mozambique
Titilope Oduyebo CDC Pregnancy Birth Defects Task Force	CDC; US ACOG, IIFPHPEWG	**Sylvanus Okogbenin** Obstetrician, epidemiology, Lassa fever/EID in pregnancy	Professor, Consultant Obstetrician, Irrua Specialist Teaching Hospital; Nigeria	**Narendra Kumar Arora**	Executive Director, The INCLEN Trust International, New Delhi, India
		Judith Absalon	Senior Director,Vaccine Clinical Research, Pfizer; US		
Cross-cutting advisors					
Marion Gruber (Regulatory) Regulatory, MI	Director, Center for Biologics Evaluation and Research (CBER) FDA; US	**Helen Rees (Regulatory)** Pregnancy registry, HIV/reproductive health, MI safety, regulatory	Professor, Wits Reproductive Health and HIV Institute, Board Chair SAHPRA; South Africa	**Daniel Brasseur (Regulatory / CEPI)**	Former CHMP-PDCO-VWP chair at EMA; CEPI consultant; EU
Ruth Karron (Ethics) Ethics of MI research	Prof., Johns Hopkins Bloomberg School of Public Health; US	**Carleigh Krubiner (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, △F; 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 + AS03 (0, 21 days)	Phase 1	TBD	Yes will conduct	Baculovirus expression YES; Adjuvant (AS03) 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; △F; 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; △F; TM	2 doses at 5 × 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 *The minimal target should be considered as a potential go/no go decision point.*	Optimistic *The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact.*	Annotations
Indication	• Prevention of severe COVID-19 disease in adults • Safe and immunogenic in pregnant and lactating women		• 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	• Pregnant women **24-36 weeks gestation** • Lactating women	• Pregnant women, **any gestational age** • Lactating women	
Maternal Safety	• No evidence of adverse pregnancy outcomes • No evidence of severe side effects • Transient and mild-moderate local reactions		• Safety in lactating women? • Breastmilk transmission?
Infant Safety	• No evidence of adverse birth outcomes • No enhanced disease in first 6 months of life		• Omitted: "No evidence of clinically significant impact on infant immunizations" as will be extremely difficult to prove
Efficacy	• **50%** of PCR-confirmed COVID-19 disease in pregnant women	• **70%** of PCR-confirmed COVID-19 disease in pregnant women	• Reduction in hospitalization, mechanical ventilation
Immunogenicity	• Achieve durable NT Ab in the mother exceeding identified biomarker	• Achieve transplacental transfer of maternal NT Ab to the infant exceeding identified biomarker	
Dose Regimen	• Non-pandemic: 1 dose prior to pregnancy, booster at 24-36 wks gestation • Pandemic: Single dose 24-36 wks gestation, booster post-partum	• Single dose given at any time during pregnancy	• 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 *The minimal target should be considered as a potential go/no go decision point.*	Optimistic *The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact.*	Annotations
Durability of protection	• Mother: 6 months	• Mother: 1 year • Infant: 3 months	• Single pregnancy vs. every pregnancy?
Route of administration	• Vaccine construct dependent		
Product	• Subunit, non-live vaccine, non-replicating	• May include novel adjuvant	
Product Stability & Storage	• 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	• 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	• Can be administered with other routinely administered maternal vaccines (DT, Tdap, Influenza) • No evidence of clinically significant impact on infant immunizations		
Presentation	• Single-dose vial, liquid formulation	• Both single-dose and multi-dose (no-thimerosol preservative) vial, liquid formulation	
EUA/WHO EUL Registration and PQ	• Outbreak: WHO prequalified and or made available under EUA/WHO EUL • LT: WHO prequalified		
Accessibility	• 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		

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

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 or lactating 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 and lactating women?
1.16 What is the efficacy of existing therapies in pregnant and lactating women?
1.17 Are pregnant and lactating 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-abortal 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-2infection 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 port-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. 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)
▪ Protein/Subunit[67] ▪ Nucleic Acid[68] ▪ Viral Vector[69] ▪ Live vaccines[70] ▪ Inactivated vaccines[71]
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, lactating/non-lactating) with the vaccine construct/platform or any of the vaccine components? **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) **3.1.2** If yes, are there any identified developmental or reproductive toxicities? If yes, describe. **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.
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 or lactating 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 or lactation?
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.

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
1.1 Are results of DART studies available or required? **1.1.1** DART studies date (or target date) of completion **1.1.2** Findings of DART studies ▪ (See also questions in Table 1. Section B.3)
C.2. Clinical Development status and plans for the vaccine in non-pregnant population
2.1 Target populations in clinical studies **2.1.1** Planned studies: planned total enrollment (answer for each: phase 1, phase 2, phase 3) **2.1.2** Ongoing studies: planned total enrollment (answer for each: phase 1, phase 2, phase 3) **2.1.3** Completed studies: total enrollment (answer for each: phase 1, phase 2, phase 3)
2.2 Location of clinical studies **2.2.1** In what countries are/will clinical studies be conducted? **2.2.2** Will studies be conducted in HIC and LMIC countries simultaneously? **2.2.3** Will approved vaccines be distributed in HIC and LMIC countries simultaneously? **2.2.4** Will vaccine be distributed in epidemic and/or endemic areas?

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 and lactating 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 or lactating 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?

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?
- 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 or lactating 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 or lactating women?
8.3 What is anticipated or known acceptance of COVID-19 vaccine by pregnant or lactating population?
8.4 Will pregnant or lactating women choose to participate in clinical vaccine studies?
8.5 Will pregnant or lactating women choose to participate in post-licensure vaccine studies?

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?

REFERENCES

[1] Sedgh G, Singh S, Hussain R. Intended and unintended pregnancies worldwide in 2012 and recent trends. *Stud Fam Plann*. 2014;45(3):301-314. doi:10.1111/j.1728-4465.2014.00393.x.

[2] National Academies of Sciences, Engineering, and Medicine 2020. Framework for Equitable Allocation of COVID-19 Vaccine. Washington, DC: The National Academies Press. https://doi.org/10.17226/25917

3 CDC National Center for Immunization and Respiratory Diseases. (14December2020). Interim clinical considerations for use of PFIzer-BioNTech COVID-19 vaccine. https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/clinical-considerations.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fcovid-19%2Finfo-by-manufacturer%2Fpfizer%2Fclinical-considerations.html

4 Pfizer-BioNTech. (December 2020). Fact sheet for healthcare providers administering vaccine/Emergency use authorization (EUA) of the Pfizer-BioNTech COVID-19 vaccine to prevent coronavirus disease 2019. https://www.cvdvaccine-us.com/images/pdf/fact-sheet-for-hcp-administering-vaccine-vaccination-providers-full-eua-prescribing-information.pdf

5 Oliver S, Gargano J, Marin M, et al. The Advisory Committee on Immunization Practices. Interim recommendation for use of Pfizer-BioNTech COVID-19 vaccine – United States, December 2020. Morb Motal Wkly Rep. ePub: 13December 2020. DOI: http://dx.doi.org/10.15585/mmwr.mm6950e2

6 Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. Update: Characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status – United States, January 22-October 3, 2020. Morb Mortal Wkly Rep 2020;69:1641-1647. DOI: http://dx.doi.org/10.15585/mmwr.mm6944e3

[7] Panagiotakopoulos L, Myers TR, Gee J, et al. SARS-CoV-2 Infection Among Hospitalized Pregnant Women: Reasons for Admission and Pregnancy Characteristics — Eight U.S. Health Care Centers, March 1–May 30, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1355–1359. DOI: http://dx.doi.org/10.15585/mmwr.mm6938e2

8 Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status — United States, January 22–June 7, 2020. Morb Mortal Wkly Rep 2020;69:769–75. http://dx.doi.org/10.15585/mmwr.mm6925a1

9 Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. Update: Characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status – United States, January 22-October 3, 2020. Morb Mortal Wkly Rep 2020;69:1641-1647. DOI: http://dx.doi.org/10.15585/mmwr.mm6944e3

10 Lokken EM, Walker CL, Delaney S, et al. Clinical characteristics of 46 pregnant women with a severe acute respiratory syndrome coronavirus 2 infection in Washington State. Am J Obstet Gynecol 2020;XX:x.exex.ex. https://doi.org/10.1016/j.ajog.2020.05.031

11 Panagiotakopoulos L, Myers TR, Gee J, et al. SARS-CoV-2 Infection Among Hospitalized Pregnant Women: Reasons for Admission and Pregnancy Characteristics — Eight U.S. Health Care Centers, March 1–May 30, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1355–1359. DOI: http://dx.doi.org/10.15585/mmwr.mm6938e2

12 Panagiotakopoulos L, Myers TR, Gee J, et al. SARS-CoV-2 Infection Among Hospitalized Pregnant Women: Reasons for Admission and Pregnancy Characteristics — Eight U.S. Health Care Centers, March 1–May 30, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1355–1359. DOI: http://dx.doi.org/10.15585/mmwr.mm6938e2

13 Allotey J, Stallings E, Bonet M. Yap M, Chatterjee S, Kew T, et al. 2020. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: Living systematic review and meta-analysis. BMJ 370:m3320. doi: 10.1136/bmj.m3320

14 Lokken EM, Walker CL, Delaney S, et al. Clinical characteristics of 46 pregnant women with a severe acute respiratory syndrome coronavirus 2 infection in Washington State. Am J Obstet Gynecol 2020;XX:x.exex.ex. https://doi.org/10.1016/j.ajog.2020.05.031

15 Lokken EM, Walker CL, Delaney S, et al. Clinical characteristics of 46 pregnant women with a severe acute respiratory syndrome coronavirus 2 infection in Washington State. Am J Obstet Gynecol 2020;XX:x.exex.ex. https://doi.org/10.1016/j.ajog.2020.05.031

16 Allotey J, Stallings E, Bonet M. Yap M, Chatterjee S, Kew T, et al. 2020. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: Living systematic review and meta-analysis. BMJ 370:m3320. doi: 10.1136/bmj.m3320

17 Knight M, Bunch K, Vousden N, et al.; UK Obstetric Surveillance System SARS-CoV-2 Infection in Pregnancy Collaborative Group. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ 2020;369:m2107.

18 Panagiotakopoulos L, Myers TR, Gee J, et al. SARS-CoV-2 Infection Among Hospitalized Pregnant Women: Reasons for Admission and Pregnancy Characteristics — Eight U.S. Health Care Centers, March 1–May 30, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1355–1359. DOI: http://dx.doi.org/10.15585/mmwr.mm6938e2

19 Allotey J, Stallings E, Bonet M. Yap M, Chatterjee S, Kew T, et al. 2020. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: Living systematic review and meta-analysis. BMJ 370:m3320. doi: 10.1136/bmj.m3320

20 Woodworth KR, Olsen EO, Neelam V, Lewis EL, Galang RR, Oduyebo T, et al. Birth and infant outcomes following laboratory-confirmed SARS-CoV-2 infection in pregnancy – SET-NET, 16 jurisdictions, March29-October 14, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1-6.

21 Khoury R, Bernstein PS, Debolt C, et al. Characteristics and outcomes of 241 births to women with severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection at five New York City medical centers. Obstet Gynecol 2020;136:273–82.

22 Knight M, Bunch K, Vousden N, et al.; UK Obstetric Surveillance System SARS-CoV-2 Infection in Pregnancy Collaborative Group. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population-based cohort study. BMJ 2020;369:m2107.

15 Knight M, Bunch K, Vousden N, et al.; UK Obstetric Surveillance System SARS-CoV-2 Infection in Pregnancy Collaborative Group. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population-based cohort study. BMJ 2020;369:m2107.

24 Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. Update: Characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status – United States, January 22-October 3, 2020. Morb Mortal Wkly Rep 2020;69:1641-1647. DOI: http://dx.doi.org/10.15585/mmwr.mm6944e3

25 Council for International Organizations of Medical Sciences. (2002). CIOMS International Ethical Guidelines for Health-Related Research Involving Humans. Retrieved from https://cioms.ch/wp-content/uploads/2016/08/International_Ethical_Guidelines_for_Biomedical_ Research_ Involving_Human_Subjects.pdf

26 UNAIDS/World Health Organization, Joint United Nations Programme on HIV/AIDS. (2007). Ethical considerations for biomedical HIV prevention trials: Guidance document. https://data.unaids.org/pub/manual/2007/jc1349_ethics_2_11_07_en.pdf

27 U.S. Food and Drug Administration (FDA). Pregnant women: scientific and ethical considerations for inclusion in clinical trials; draft guidance for industry, April 2018. https://www.fda.gov/media/112195/download

28 U.S. Food and Drug Administration (FDA). Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry, June 2020. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19

29 The American College of Obstetrician and Gynecologists' Immunization, Infectious Disease, and Public Health Preparedness Expert Work Group. (13December2020). Vaccinating pregnant and lactating patients against COVID-19. https://www.acog.org/en/clinical/clinical-guidance/practice-advisory/articles/2020/12/vaccinating-Pregnant-and-Lactating-Patients-Against-COVID-19

30 CDC National Center for Immunization and Respiratory Diseases. (14December2020). Interim clinical considerations for use of Pfizer-BioNTech COVID-19 vaccine. https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/clinical-considerations.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fcovid-19%2Finfo-by-manufacturer%2Fpfizer%2Fclinical-considerations.html

31 Pfizer and Biontech commence global clinical trial to evaluate covid-19 vaccine in pregnant women. 18February2021. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-commence-global-clinical-trial-evaluate

32 Kolata G. Johnson & Johnson has planned trials of its vaccine that will include infants.28February2021. https://www.nytimes.com/2021/02/28/world/johnson-and-johnson-vaccine-testing-children.html

33 The American College of Obstetrician and Gynecologists' Immunization, Infectious Disease, and Public Health Preparedness Expert Work Group. (13December2020). Vaccinating pregnant and lactating patients against COVID-19. https://www.acog.org/en/clinical/clinical-guidance/practice-advisory/articles/2020/12/vaccinating-Pregnant-and-Lactating-Patients-Against-COVID-19

34 The PREVENT Working Group. Pregnant Women & Vaccines Against Emerging Epidemic Threats: Ethics Guidance for Preparedness, Research, and Response. Baltimore, MD: September 2018. http://vax.pregnancyethics.org/prevent-guidance/

35 Pandemic Influenza Risk Management: A WHO guide to inform and harmonize national and international pandemic preparedness and response. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. https://www.who.int/influenza/preparedness/pandemic/influenza_risk_management_update2017/en/

36 National Academies of Sciences, Engineering, and Medicine 2020. Framework for Equitable Allocation of COVID-19 Vaccine. Washington, DC: The National Academies Press. https://doi.org/10.17226/25917

37 American College of Obstetricians and Gynecologists. Clinical Practice Advisory: Novel Coronavirus 2019 (COVID-19). September 2020. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/03/novel-coronavirus-2019

38 Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT). http://vax.pregnancyethics.org/

39 Society for Maternal Fetal-Medicine. Society for Maternal-Fetal Medicine (SMFM) Statement: SARS-CoV-2 Vaccination in Pregnancy. December 1, 2020. https://s3.amazonaws.com/cdn.smfm.org/media/2591/SMFM_Vaccine_Statement_12-1-20_(final).pdf

40 World Health Organization. WHO Target Product Profiles for COVID-19 Vaccines. (April, 2020). https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines

41 World Health Organization. WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination. 14 September 2020. https://apps.who.int/iris/bitstream/handle/10665/334299/WHO-2019-nCoV-SAGE_Framework-Allocation_and_prioritization-2020.1-eng.pdf?ua=1

42 National Academies of Sciences, Engineering, and Medicine 2020. Framework for Equitable Allocation of COVID-19 Vaccine. Washington, DC: The National Academies Press. https://doi.org/10.17226/25917

43 Mbaeyi S, and the ACIP COVID-19 Vaccines Working Group. (12December2020). Use of Pfizer-BioNTech COVID-19 vaccine: clinical considerations. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2020-12/slides-12-12/COVID-03-Mbaeyi.pdf

44 The American College of Obstetrician and Gynecologists' Immunization, Infectious Disease, and Public Health Preparedness Expert Work Group. (13December2020). Vaccinating pregnant and lactating patients against COVID-19. https://www.acog.org/en/clinical/clinical-guidance/practice-advisory/articles/2020/12/vaccinating-Pregnant-and-Lactating-Patients-Against-COVID-19

45 The Access to COVID-19 Tools (ACT) Accelerator. https://www.who.int/initiatives/act-accelerator

46 World Health Organization. (20 November 2017) Stakeholders meeting on maternal interventions vigilance: safety monitoring and surveillance in vaccine and other research settings. https://apps.who.int/iris/bitstream/handle/10665/260246/WHO-EMP-2018.1-eng.pdf

47 Pan American Health Organization. (3 December 2020) Immunization Program during the COVID-19 Pandemic. https://www.paho.org/en/immunization-program-during-covid-19-pandemic

[48] National Institutes of Health, Office of Disease Prevention. 16June2020. Fact sheet: Explaining Operation Warp Speed. https://prevention.nih.gov/news-events/news-releases/2020/06/fact-sheet-explaining-operation-warp-speed

49 Infectious Diseases Clinical Research Consortium. https://idcrc.org/

50 Immunizing Pregnant Women and Infants (IMPRINT) https://www.imprint-network.co.uk

51 Matthews S, et al. Advisory Board Technical Consultation for COVAX Maternal Immunization Work Group: Maternal Immunization Post-Licensure Safety Needs for Pregnant Women and their Infants Technical Consultation Report. 2021. http://safeinpregnancy.org/resources/Report_Advisory%20Board%20Survey%20COVAX_FINAL_pdf.pdf

52 WHO Target Product Profiles for COVID-19 Vaccines. https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines#:~:text=This%20Target%20Product%20Profile%20(TPP,with%20rapid%20onset%20of%20immunity

53 Dong L, Tian J, He S, et al. Possible Vertical Transmission of SARS-CoV-2 From an Infected Mother to Her Newborn. JAMA. 2020;323(18):1846–1848.

54 Facchetti et al. www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30327-3/fulltext

55 Flannery DD, Gouma S, Dhudasia MB, et al. Assessment of Maternal and Neonatal Cord Blood SARS-CoV-2 Antibodies and Placental Transfer Ratios. *JAMA Pediatr.* Published online January 29, 2021. doi:10.1001/jamapediatrics.2021.0038

56 Edlow AG, Li JZ, Collier AY, Atyeo C, James KE, Boatin AA, et al. Assessment of Maternal and Neonatal SARS-CoV-2 Viral Load, Transplacental Antibody Transfer, and Placental Pathology in Pregnancies During the COVID-19 Pandemic. *JAMA Netw Open*. 2020 Dec 1;3(12):e2030455. doi: 10.1001/jamanetworkopen.2020.30455. PMID: 33351086; PMCID: PMC7756241.

57 Benefit-Risk Assessment of VAccies by TechnolOgy (BRAVATO (ex-V3SWG) https://brightoncollaboration.us/bravato/

58 Kim D, Robertson JS, Excler JL, Condit R, East PA, Gurwith M, et al. The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of nucleic acid (RNA and DNA) vaccines. Vaccine 2020;38(2020):5556–5561. https://doi.org/10.1016/j.vaccine.2020.06.017

59 Kochhar S, Kim D, Exler JL, Condit RC, Robertson JS, Drew, S, et al. The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of protein vaccines. Vaccine 2020;38:5735-5739. https://doi.org/10.1016/j.vaccine.2020.06.044

60 Condit RC, Kim D, Robertson JS, Excler JL, Gurwith M, Monath TP, et al.The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of viral vector vaccines. Vaccine 2020; 38(49):7708-7715. https://doi.org/10.1016/j.vaccine.2020.08.009

61 Kochhar S, Excler JL, Kim D, Robertson, Fast PE, Condit R, et al. The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of inactivated viral vaccines. Vaccine 2020;38(39):6184-6189. https://doi.org/10.1016/j.vaccine.2020.07.028

62 Gurwith M, Condit RC, Excler JL, Robertson JC, Kim D, Fast PE, et al. The Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG) standardized template for collection of key information for benefit-risk assessment of live-attenuated viral vaccines. Vaccine 2020;38(49):7702-7707. https://doi.org/10.1016/j.vaccine.2020.09.042

63 US Food and Drug Administration. Development and Licensure of Vaccines to Prevent COVID-19 Guidance for Industry. June 2020. https://www.fda.gov/media/139638/download.

64 US Food and Drug Administration. Development and Licensure of Vaccines to Prevent COVID-19 Guidance for Industry. June 2020. https://www.fda.gov/media/139638/download.

65 UK Medicines and Healthcare products Regulatory Agency. Information for healthcare professionals on Pfizer/BioNTech COVID-19 vaccine: Regulation 174 information for UK healthcare professionals. 28January2021. https://www.gov.uk/government/publications/regulatory-approval-of-

pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine

66 Sobanjo-ter Meulen A and Saville M. (16December2020) Accelerating access to COVID-19 vaccine for pregnant and lactating women – what do developers need to know? Meeting Report. file:///C:/Users/shiel/Downloads/2020%2001%2022_COVAX%20Maternal%20Immunization%20Working%20Group%20Webinar%20Report_final.pdf

67 Kochhar S, Kim D, Exler JL, Condit RC, Robertson JS, Drew, S, et al. The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of protein vaccines. Vaccine 2020;38:5735-5739. https://doi.org/10.1016/j.vaccine.2020.06.044

68 Kim D, Robertson JS, Excler JL, Condit R, East PA, Gurwith M, et al. The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of nucleic acid (RNA and DNA) vaccines. Vaccine 2020;38(2020):5556–5561. https://doi.org/10.1016/j.vaccine.2020.06.017

69 Condit RC, Kim D, Robertson JS, Excler JL, Gurwith M, Monath TP, et al.The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of viral vector vaccines. Vaccine 2020; 38(49):7708-7715. https://doi.org/10.1016/j.vaccine.2020.08.009

70 Gurwith M, Condit RC, Excler JL, Robertson JC, Kim D, Fast PE, et al. The Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG) standardized template for collection of key information for benefit-risk assessment of live-attenuated viral vaccines. Vaccine 2020;38(49):7702-7707. https://doi.org/10.1016/j.vaccine.2020.09.042

71 Kochhar S, Excler JL, Kim D, Robertson, Fast PE, Condit R, et al. The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of inactivated viral vaccines. Vaccine 2020;38(39):6184-6189. https://doi.org/10.1016/j.vaccine.2020.07.028

57 Sahin, U., Muik, A., Derhovanessian, E. et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature 586, 594–599 (2020). https://doi.org/10.1038/s41586-020-2814-7

58 Anderson EJ, Rouphael NG, et al. Safety and immunogenicity of SRAS0CoV-2 mRNA-1273 vaccine in older adults. NEJM Sept, 2020; DOI: 10.1056/NEJMoa2028436

59 Mercado, N.B., Zahn, R., Wegmann, F. et al. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. Nature 586, 583–588 (2020). https://doi.org/10.1038/s41586-020-2607-z

60 Folegatti PM, Ewere KJ, Aley PK, Angus B, Becker S, Belij-Rammerstrofer, et al. Safety and immunogenicity of the ChAdOx1 nCOV-19 vaccine against SARS-CoV-2: a preliminary report of a phase ½, single-blind, randomized controlled trial. The Lancet 2020;396(10249):467-478. DOI:https://doi.org/10.1016/S0140-6736(20)31604-4

61 Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, et al. Phase1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. NEJM 2020. DOI: 10.1056/NEJMoa2026920

62 Sanofi Pasteur and GlaxoSmithKline. Study of recombinant protein vaccine formulations against COVID-19 in healthy adults 18 years of age and older. ClinicalTrials.gov: NCT04537208. https://clinicaltrials.gov/ct2/show/NCT04537208.

63 CSL. CSL to manufacture and supply University of Queensland and Oxford University vaccine candidates for Australia. 06 September 2020. https://www.csl.com/news/2020/20200907-csl-to-manufacture-and-supply-uq-and-ou-vaccine-candidates-for-australia

64 Clover Biopharmaceuticals. Clover announces positive preclinical data and updates on Phase 1 study for its adjuvanted S-Trimer COVID-19 vaccine candidate. 25 September 2020. http://www.cloverbiopharma.com/index.php?m=content&c=index&a=show&catid=11&id=50

65 CureVac. CureVac initiates phase 2a clinical trial of COVID-19 vaccine candidate. Press release. 29 September 2020. https://www.curevac.com/en/2020/09/29/curevac-initiates-phase-2a-clinical-trial-of-covid-19-vaccine-candidate/

66 Merck Sharp & Dohme Corporation. Dose ranging trial to assess safety and immunogenicity of V590 (COVID-19 Vaccine) in healthy adults (V590-001). Clinical Trials.gov: NCT04569786. https://clinicaltrials.gov/ct2/show/NCT04569786