



COVAX Maternal Immunization Working Group Webinar

Accelerating Access to COVID-19 Vaccine for Pregnant and Lactating Women – What do Developers Need to Know?

December 16, 2020

Meeting Report

EXECUTIVE SUMMARY

On December 16, 2020 COVAX, supported by the Coalition for Epidemic Preparedness Innovations (CEPI), the Global Alliance for Vaccines and Immunizations (GAVI), and the World Health Organization (WHO), hosted a webinar organized by the COVAX Maternal Immunization Working Group 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.

Dr Melanie Saville (CEPI) and Dr Ajoke Sobanjo-ter Meulen (Bill & Melinda Gates Foundation and COVAX Maternal Immunization Working Group Co-Chair) welcomed everyone to the meeting and provided background on the current status of COVID-19 vaccine research. As pregnant 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 received the vaccine. Emergency use authorization (EUA) for COVID-19 vaccines also differ by country, with vaccination of pregnant and lactating women permitted under the US EUA, but at the time of this event, not recommended in the UK due to lack of safety and developmental and reproductive toxicology (DART) data in these populations (this has been updated since the webinar took place to include recommendation of administration in pregnant women where potential benefits outweigh potential risks:

<https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine>).

Dr Titilope Oduyebo (US Centers for Disease Control and Prevention [CDC]) summarized data which demonstrated an increased relative risk of severe COVID-19 in pregnant women, with higher likelihood of ICU admission or mechanical ventilation compared with non-pregnant women, although the absolute risk remains low. Maternal age ≥ 35 years, body mass index $\geq 30\text{kg/m}^2$ and underlying medical conditions such as pre-existing type 2 diabetes and hypertension were identified as risk factors for severe COVID-19 in pregnancy. Based on the available evidence, the US CDC now classifies pregnant women as a population who is at increased risk of severe COVID-19.

Dr Flor Munoz (Baylor College of Medicine and Co-Chair of the Maternal Immunization Working Group) discussed the importance of harmonizing methods for evaluating the safety of COVID-19 vaccines during pregnancy. The decision to immunize pregnant women should be based on balance of risk from disease versus potential risk of the vaccine. She outlined some of the recommendations for influenza vaccination in pregnant women subsequent to the 2009 influenza pandemic. Additionally, she highlighted some of the resources and safety assessment tools already available through the WHO which can help to harmonize data collection and assessment of COVID-19 vaccines in pregnant women.

Prof Beate Kampmann (London School of Hygiene and Tropical Medicine) then discussed the best time for pregnant women to be included in COVID-19 vaccine assessments. Final DART data were not available at the time of the webinar for any COVID-19 vaccines, but available information is reassuring and studies are ongoing. While pregnant women should be excluded from Phase 1 studies, it would be possible to include them in Phase 2 if safety data are already available from vaccines that use the same platform. Phases 3 and 4 are the best options for inclusion of pregnant women, with appropriate follow-up to monitor maternal and infant outcomes. Lactating women should be considered separately from pregnant women. While there is evidence of transmission of COVID-19 IgG and IgA in breast milk, vaccination should not be withheld for lactating women who otherwise meet vaccination criteria.

Dr Jessica Andriesen (Fred Hutchinson Institute and COVID-19 Prevention Network) highlighted the need to standardize outcome reporting of pregnancies that occur in participants of Phase 2-3 clinical trials and discussed the data currently being collected in Phase 3 COVID-19 vaccine trials conducted as part of Operation Warp Speed. These trials have similar study designs, however, they differ in terms of pregnancy outcomes assessed, as pregnant women were not intended to be included in the study populations. She emphasized the need for future trials to standardize data collection and outcome measures and to bridge existing gaps by providing robust data on the impact of vaccination in pregnant and lactating women.

After a brief question and answer session, where the potential challenges of enrollment of pregnant women in clinical trials were discussed, Prof Andy Stergachis (University of Washington) provided a summary of considerations for post-licensure safety surveillance in pregnant women. He highlighted the key role of pregnancy registries and active surveillance, and once again emphasized the need for standardized protocols and harmonized procedures. Finally, he highlighted the need for

timely communication of findings to mitigate vaccine hesitancy.

Dr Deus Mubangizi (WHO) then described the WHO prequalification program and emergency use listing (EUL) to expedite access to health products during emergency situations. He provided details of the currently available documents and guidelines for COVID-19 vaccines, and explained that alignment activities are still ongoing, particularly for assessment and in-country vaccine approval.

Dr Narendra K. Arora (INCLIN Trust International) subsequently discussed the unique challenges of assessing vaccine safety in low and middle income countries (LMIC) using India as an example. The roll-out of COVID-19 vaccines across healthcare workers in India presents a unique opportunity to analyze data from pregnant healthcare workers who will receive the vaccine. Dr Arora highlighted the importance of having standardized procedures for surveillance, as well as including a broader diversity of experts to assess adverse events following immunization (AEFIs), and collaboration between expanded programs on immunization (EPI) and maternal, newborn, child, and adolescent health (MNCAH) programs. He discussed initiatives to measure background rates of pregnancy outcomes, which have highlighted areas with need for improvement, such as harmonization, documentation and training.

The webinar ended with a panel discussion, which highlighted the need for high quality data on COVID-19 vaccination in pregnant women going forward. The key needs for maternal immunization include:

1. Harmonization of existing and new safety surveillance protocols, data collection approaches, and methodologies to leverage diverse data sources including inadvertent vaccine exposure in pregnant women
2. Inclusion of pregnant women in clinical trials early in vaccine development in pandemic situations
3. Collection of high-quality and communication of findings vaccine safety and immunogenicity in data in pregnancy to enable informed decision making by healthcare providers and pregnant women
4. Risk-benefit analyses at both the population and individual level
5. Maintaining highly collaborative efforts and coordination within the healthcare and surveillance systems in preparation for vaccine rollout scenarios including pregnant women
6. Consideration of the specific challenges in safety surveillance and recording pregnancy outcomes faced by LMICs, and the need to collect additional

epidemiologic data to assess COVID-19 risk in pregnant women in these countries

7. Continued effective education and engagement of healthcare professionals
8. Enhanced communication with all stakeholders, including vaccine developers, healthcare providers, pregnant women, and their families.

MEETING AGENDA

Time (PDT)	Session	Speaker
7:30 am PT	Welcome	Melanie Saville
7:35 am PT	Workshop Introduction	Ajoke Sobanjo-ter Meulen
7:40 am PT	COVID-19 in pregnancy: Pregnancy as a risk factor for severe COVID-19 disease	Titilope Oduyebo
7:50 am PT	The need for a harmonized methodology to evaluate SARS-CoV-2 vaccines in pregnancy during pandemic vaccine development and implementation	Flor Munoz
8:00 am PT	Preclinical and clinical evaluation of COVID-19 vaccines in pregnant and lactating women	Beate Kampmann
8:10 am PT	Standardized outcome reporting in pregnant women exposed to COVID-19 vaccines in clinical trials	Jessica Andriesen
8:20 am PT	Q&A (with speakers)	Ajoke Sobanjo-ter Meulen
8:30 am PT	Break	
8:35 am PT	Post-licensure COVID-19 vaccine safety surveillance in pregnant women	Andy Stergachis
8:45 am PT	WHO evaluation strategy for COVID-19 vaccines	Deus Mubangizi
8:55 am PT	How should safety be assessed in pregnant women exposed to COVID-19 vaccines after emergency use approval in LMIC?	Narendra Arora
9:05 am PT	Break	
	Panel Discussion	
9:10 am PT	Key Question for all panelists: What is the #1 issue we must get right in our urgent effort to ensure that pregnant women have access to a COVID-19 vaccine? Data sharing Pregnancy trials EUA and Pregnancy High risk groups - Health care workers	Introduction by Ruth Karron Moderated by Ruth Karron Q&A curator Chrissie Jones
9:50 am PT	Wrap-up and Next Steps	Ajoke Sobanjo-ter Meulen & Flor Munoz
10:00 am PT	Webinar end	

Meeting Highlights

Welcome and Meeting Objectives

Dr Melanie Saville, Director of Vaccine Research and Development at CEPI welcomed attendees and introduced the webinar. She explained the role of COVAX as a group of organizations aiming to accelerate development of COVID-19 vaccines and to deliver up to two billion vaccine doses to participating countries, irrespective of their ability to pay. Vaccine development has moved forward at an unprecedented speed, and with the first emergency use authorizations (EUAs) issued in December 2020 in some countries including the United States and the United Kingdom, it is important to roll out the vaccine to populations who are most in need. One population which is often overlooked is pregnant and lactating women. Accordingly, the goal of this webinar was to bring together experts on maternal immunization with vaccine developers to have an open discussion on how to ensure plans are in place to provide safe and effective COVID-19 vaccines to pregnant and lactating women.

Dr Ajoke Sobanjo-ter Meulen (Co-Chair of the COVAX Maternal Immunization Working Group and Maternal Immunization Lead at the Bill and Melinda Gates Foundation) provided background on the current status of COVID-19 vaccine trials, and the potential for inclusion of pregnant women. To date, pregnant women have been excluded from Phase 3 clinical trials and developmental and reproductive toxicology (DART) studies had not been finalized at the time of the webinar. Additionally, a number of the COVID-19 vaccines in development are based on new platforms for which very limited clinical data are available. Despite the lack of final DART data, the Pfizer vaccine EUA granted in the United States in early December uses permissive wording to include all persons >16 years of age, with no contraindication for pregnant women (full details available from: <https://www.fda.gov/media/144414/download>). In contrast, the UK regulatory agency chose to exclude pregnant women from their recommendations, as no clinical data, apart from inadvertent exposure, were available in this population (full details available from: <https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19>). The US Advisory Committee on Immunization Practices (ACIP) recognizes the need to protect pregnant women from COVID-19, and allows these women to choose the best

option for them, after an optional discussion of the risks and benefits with their health care providers (for further details, see <https://www.cdc.gov/vaccines/covid-19/info-by-manufacturer/pfizer/clinical-considerations.html>).

As many females of child-bearing age will be vaccinated during the roll-out of COVID-19 vaccines to healthcare workers, this will provide a unique opportunity to collect safety data on COVID-19 vaccination in pregnancy in individuals at high risk of exposure to the disease. To date, there are only limited data from inadvertent exposure to pregnant women during Phase 3 trials. Robust data collection in real-world situations and specific studies including pregnant women are needed.

Dr Sobanjo-ter Meulen introduced the COVAX Maternal Immunization Working Group, which has the goal of identifying research and development needs towards supporting a COVID-19 vaccine recommendation for pregnant women. She outlined the objectives of the working group, which fall under three key activities:

1. Product mapping, which includes review of the candidate vaccines and their suitability/readiness for maternal immunization
2. Pre-clinical/clinical studies, which includes assessment of vaccine evaluation needs
3. Safety/post-marketing safety assessments in pregnant women and their infants.

The working group also focuses on discussing the regulatory and ethical needs for inclusion of pregnant women in COVID-19 vaccine development and deployment.

Pregnancy as a Risk Factor for Severe COVID-19

Dr Titilope Oduyebo, Senior Medical Officer in the Epidemiology and Vaccines Task Force at the US Centers for Disease Control and Prevention (CDC) presented the currently available data on the susceptibility to infection and disease severity in pregnant women with COVID-19. Pregnant women may be at increased risk of severe disease due to physiological changes during pregnancy, including increased heart rate and oxygen consumption, decreased lung capacity, and a reduction in cell-mediated immunity. Increased disease severity during pregnancy has been observed with other viral respiratory infections, such as influenza. A recent living systematic review¹ of 77 studies identified the following factors as risk factors for severe COVID-19 during pregnancy:

- Maternal age ≥ 35 years
- Body mass index ≥ 30 kg/m²
- Underlying medical conditions such as pre-existing type 2 diabetes and chronic hypertension

When compared with non-pregnant women, pregnant women were significantly more likely to require ICU admission or invasive ventilation. No significant difference was observed in all-cause mortality; however, the overall mortality rate was low in both groups. This literature review is currently being updated with a large number of studies published through October 6, 2020, with results showing a continued increased risk of ICU admission and invasive ventilation after addition of these extra studies.

Similar findings were also observed in a recent CDC analysis of SARS-CoV-2 infection by pregnancy status², where symptomatic pregnant women had significantly higher risk of:

- ICU admission – adjusted relative risk (aRR) = 3.0
- Mechanical ventilation – aRR = 2.9
- Extracorporeal membrane oxygenation (ECMO) – aRR = 2.4
- Death – aRR = 1.7

This case surveillance data had the advantage of including a large number of individuals, which provided statistical power to study rare outcomes like maternal death. However, there were also a number of limitations including a large number of cases with missing data on pregnancy status, and no data on pregnancy outcomes.

Two studies in the review also reported increased odds of pre-term birth (<37 weeks gestation) in pregnant women with COVID-19. This conclusion was, however, mainly based on results from one small study of severely ill women performed early in the pandemic and during a stressful lockdown, therefore the findings should be interpreted with caution. Some more recent studies investigating pre-term birth have shown inconsistent data. Recently published data from CDC indicates an increased prevalence of pre-term birth in pregnant women with COVID-19, although the role of COVID-19 versus other pre-disposing factors remains unknown. The risks may also be different in other countries and resource settings.

Based on the available evidence, the CDC revised its risk categorization on November 2, 2020 to state that pregnant women are at increased risk of severe COVID-19 illness compared to non-pregnant women.³

References

1. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, Debenham L, Llavall AC, Dixit A, Zhou D, Balaji R, Lee SI, Qiu X, Yuan M, Coomar D, van Wely M, van Leeuwen E, Kostova E, Kunst H, Khalil A, Tiberi S, Brizuela V, Broutet N, Kara E, Kim CR, Thorson A, Oladapo OT, Mofenson L, Zamora J, Thangaratnam S; for PregCOV-19 Living Systematic Review Consortium. *Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020 Sep 1;370:m3320.*
2. Zambrano LD, Ellington S, Strid P, 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. MMWR Morb Mortal Wkly Rep 2020;69:1641–1647.*
3. Centers for Disease Control and Prevention. *COVID-19. People with Certain Medical Conditions. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html#pregnancy>*

Harmonized Methodology for Evaluating SARS-CoV-2 Vaccines in Pregnancy

Dr Flor Munoz, Associate Professor of Pediatrics, Molecular Virology, and Microbiology at Baylor College of Medicine and Co-Chair of the COVAX-Maternal Immunization WG, reiterated that while there are currently 236 vaccines across 9 different platforms in development for COVID-19 (see <https://www.covid-19vaccinetracker.org/>), pregnant women have not been included in clinical trials.

The WHO statement on vaccines in pregnancy (available from: https://www.who.int/immunization/documents/positionpapers_intro/en/) states that pregnancy should not deter women from receiving vaccines that are safe and will protect both her health and that of her unborn child when there is a high risk for exposure and potential risk for the mother and/or the fetus. Recommendations on immunization during pregnancy have therefore focused on assessment of the risk from disease (i.e. risk of exposure and harm to the mother and/or fetus) versus the potential risk and benefits from the vaccine. Adverse events following immunization (AEFIs), whether they are related or not, can have substantial impact on vaccine confidence, and should

also be considered in any risk/benefit analysis. Current guidance regarding COVID-19 vaccination during pregnancy varies in the US and UK, as outlined by Dr Sobanjo-ter Meulen in the introduction. There are 3 possible scenarios where pregnant women could receive a COVID-19 vaccine at this time and during which safety and efficacy data could be collected – one is through participation in a clinical trial that includes pregnant women (which is not available at this time) or inadvertent exposure to vaccination when a pregnancy occurs while participating in clinical trial that excludes pregnant women, the second is vaccination after vaccine licensure, and the third is vaccination in the context of permissive use in pregnancy of a vaccine authorized for emergency use during the pandemic. Surveillance systems for each of these scenarios differ, but each present opportunities to learn more about COVID-19 vaccination in pregnancy. Professors Andriesen and Stergachis will later discuss the mechanisms for safety assessment in the context of unanticipated pregnancy while participating in a non-pregnancy study, and post-licensure surveillance, respectively.

In the context of vaccination of pregnant women during EUA conditions, the proposed safety surveillance plans in the US include leveraging existing active and passive surveillance systems, assessing individual cases, and large linked database monitoring systems. Specifically, the V-safe database (<https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafe.html>) is an enhanced surveillance system that will include the evaluation of COVID-19 vaccine safety in pregnant women and follow pregnancies to assess their outcome. In general, safety surveillance systems should include the following components:

- Detection of AEFIs and adverse events of special interest (AESIs)
- Verification of vaccination status
- Causality assessments
- Analysis of observed versus expected number of events
- Communication of risk to healthcare professionals and the public

We have the benefit of previous experience of implementation of influenza vaccination in pregnant women following the 2009 influenza pandemic, which may prove valuable during this COVID-19 pandemic. The instruction manual for the implementation of influenza vaccine in pregnancy published in 2016 by the WHO (available from: http://www.who.int/immunization/research/development/influenza_maternal_immunization/en/index1.html) provides planning guidance, data collection, and case assessment tools which can help harmonize data collection and safety

assessments, and generate robust data on the safety of COVID-19 vaccination in pregnant women.

The COVAX Maternal Immunization Working Group supports inclusion of pregnant women in COVID-19 vaccine development and implementation efforts and plan to support the development of various maternal immunization modules aimed at providing harmonized guidance, data collection tools, and causality assessments for the assessment of vaccine safety in pregnant women. Having an established safety surveillance system for pregnant women who receive COVID-19 vaccines under any of the scenarios described is necessary based on the following considerations:

- Need to improve our understanding of vaccine(s) safety profile
- Need to document safety in context of pregnancy risks (mother and infant)
- Generating evidence of vaccine safety based on population-based data
- Detection of common (> 1/10,000 vaccinees) and rare events (< 1/100,000 vaccinees)
- Importance to consider the complexity of vaccine schedules: vaccines given to pregnant women and new vaccinees
- Evidence-based decision making
- Building and maintaining confidence among providers and vaccine recipients
- Improving existing surveillance systems (e.g. linked electronic health records databases) or developing targeted surveillance systems
- Utilization of harmonized and consistent case definitions, data collection tools for comparability
- Supporting data sharing and international collaboration
- Establishing a successful maternal immunization program

Preclinical and Clinical Evaluation of COVID-19 Vaccines in Pregnant and Lactating Women

Prof Beate Kampmann, Professor of Paediatric Infection and Immunity at the London School of Hygiene and Tropical Medicine, provided a perspective on the considerations to determine the most suitable vaccine candidate and timing for enrollment of pregnant women in COVID-19 vaccine clinical trials. For most candidate vaccines, reproductive toxicology data should be available before pregnant women are considered for inclusion in clinical trials, irrespective of the vaccine platform. Developmental and reproductive toxicity (DART) studies are ongoing, but given their

dependence on gestational lengths these take time to complete and no final data were publicly available at the time of the webinar. An overview of the stages of clinical development in relation to consideration for inclusion of pregnant women is outlined below:

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

The best time to include pregnant women in clinical evaluations also varies depending on specific vaccine platforms. Replicating viral vector and live-attenuated vaccines should be avoided due to potential increased risk in pregnancy, whereas protein subunit, inactivated, and non-replicating viral vector platforms may be more suitable, as clinical safety data are available from other vaccines using these platforms. Modified messenger RNA (mRNA) vaccines may also be suitable, although data are still limited for this vaccine platform.

Regarding lactating women, data are not currently sufficient to finally conclude that there is no transmission of COVID-19 through breastmilk, but SARS-CoV-2 IgA and IgG can be

detected in breastmilk.¹ The COVAX working group members opined that COVID-19 vaccines should not be withheld from lactating women who otherwise meet the criteria for vaccination, as theoretical safety concerns do not outweigh the potential benefits of vaccination.

A number of questions remain regarding COVID-19 vaccination in pregnant and lactating women, and additional data collection under harmonized protocols can help answer these questions, providing confidence for both vaccine developers and pregnant and lactating women.

References

1. Groß R, Conzelmann C, Müller J, et al. Detection of SARS-CoV-2 in human breastmilk. *Lancet*. 2020;395(10239):1757-1758

Standardizing Outcome Reporting in Pregnant Women Exposed to COVID-19 Vaccines in Clinical Trials

Dr Jessica Andriesen, Associate Director of Statistical and Data Management Center Operations at the COVID-19 Prevention Network (CoVPN), introduced the data that is being collected when pregnancies occur in studies of vaccines conducted as part of Operation Warp Speed (OWS), a US government collaboration with multiple pharmaceutical companies conducting Phase 3 studies of COVID-19 vaccines. The trials have standardized structures and enroll approximately 30,000 adults aged ≥18 years who are at risk of SARS-CoV-2 infection and COVID-19 diseases. They aim to have 25% of participants aged > 55 years. The trials are randomized 1:1 or 2:1 to receive vaccine vs. placebo, with potential for stratification within risk strata (e.g. age groups). All the trials have the primary endpoint of virologically-confirmed symptomatic disease, with follow-up periods of up to 25 months, although the follow-up period may prove difficult for placebo recipients given the roll-out of COVID-19 vaccines under EUA. As the studies exclude pregnant women, very limited data exist for this population, with the only data to date coming from inadvertent exposure during trials (this includes a small number of women, with double digit numbers across all trials). Currently Month 4 visits are expected between November 2020 to February 2021 for mRNA vaccine trials, and in Q1 2021 for viral vector trials, so individual participants' time on trial as of the time of this workshop has not been very long.

Additionally, as the trials have not been designed to assess safety or impact in pregnant women, pregnancy data and outcomes collected during the trials varies, with gaps both in screening and post-pregnancy outcomes. In the studies presented by Dr. Andriesen, the data collection tools for assessment of inadvertent pregnancies utilized by five different manufacturers supported by OWS were reviewed. Among these, the Moderna and Sanofi vaccine trials capture the most data on pregnancy outcomes, including infant follow-up data beyond delivery. Some trials only assess the outcome of the pregnancy as live birth or not. The level of detail of the data collected is highly variable. Future trials should bridge the existing gaps and standardize data collection methods to allow cross-study comparison and analysis. The standardization of data collection methods will also enable more meaningful data to be collected from trials not designed specifically for pregnant women, but during which incident pregnancies will occur.

Part 1: Question and Answer Session

The following questions were discussed in the Q&A session at the end of Part 1 of the webinar:

Q. What is the current status of DART studies?

A. DART study timelines cannot be compressed due to fixed gestational periods of the animals used in the studies. DART studies are currently underway for vaccines in Phase 3 in the United States and first results are expected later in December 2020 or in January 2021

Q. Is it likely that pregnant women will consent to participate in clinical trials, particularly for a new vaccine product?

A. Pregnant women have previously participated in clinical vaccine trials, including pandemic influenza in 2009, Tdap, and vaccines specifically targeting pregnant women, such as RSV and GBS. As with any study, the potential risks and benefits should be considered and discussed with potential volunteers so pregnant women and their obstetric providers can make an informed decision to participate. Pregnant women who are at higher risk due to occupational exposure or comorbidities may be more willing to participate. There is a need for minimum data for both DART data and safety data in non-pregnant women, prior to inclusion of pregnant women in vaccine trials or permissive vaccination. Additionally, some vaccine platforms have more data available for non-pregnant or even pregnant populations

and may therefore require less additional data collection than others.

Q. What is the available evidence for deferring pregnancy for 2–3 months following receipt of a COVID-19 vaccine?

A. There are currently very limited data available on the effects of COVID-19 vaccines in pregnant women. Current advice is based on data from pregnant women inadvertently vaccinated, assessment of risk/benefit profiles, and expert opinion. More data are becoming available all the time, and based on the current risk/benefit profiles there is no evidence of the need to delay pregnancy or vaccination of pregnant women, although this population are not currently being considered for imminent mass vaccination.

Additionally, with the roll-out of COVID-19 vaccines in the US, including for pregnant and lactating women who wish to be vaccinated, data from pregnancy registries (<https://www.fda.gov/science-research/womens-health-research/list-pregnancy-exposure-registries>) will become increasingly available and provide valuable outcome data in these populations

Q. What can we do about cultural and social barriers to vaccination of pregnant women?

A. The key is identification of stakeholders and prospective recognition that different stakeholders may have different issues. It is paramount that the interests of pregnant women are addressed based on information that we have available.

Post-Licensure COVID-19 Safety Surveillance in Pregnant Women

Prof Andy Stergachis, Professor of Pharmacy and Global Health at the University of Washington, emphasized the essential nature of post-EUA and post-licensure safety surveillance of COVID-19 vaccine use in pregnant women, given the current knowledge gaps and exclusion of this population from clinical trials. Standard approaches to post-licensure vaccine safety evaluation involves passive and active surveillance. Among active surveillance methods, pregnancy registries are commonly used during the post-licensure phase to monitor the safety of vaccines and other medicines used during pregnancy. Pregnancy registries are a key surveillance tool as they can actively collect data on exposures and outcomes, and are prospective thereby avoiding recall and reporting biases. While these registries are most commonly used in high income countries, some low- and middle-income countries (LMICs) also successfully use them. Other important active surveillance approaches

include follow-up of vaccinated women of childbearing age through cohort event monitoring and databases. Importantly, databases can play an important role in post-licensure safety surveillance in those instances where there is confidence in the quality of data and the ability to link records across time and between mother and child. It is important to implement these registries across geographic areas and populations. Numerous stakeholders are relevant to pregnancy safety surveillance, including:

- WHO
- National medicine regulators
- Vaccine manufacturers
- Public health programs
- Brighton Collaboration
- Research and other networks
- Donor organizations
- Other non-government organizations

Overall, key considerations for success of post-licensure safety surveillance requires standardized, harmonized protocols to allow data pooling, collaboration between stakeholders, causality assessments, and timely communication of findings to mitigate potential vaccine hesitancy. He concluded by saying that data from post-licensure and post-EUA authorization safety surveillance is critical for ongoing benefit-risk assessment by regulators and for practice guidelines.

WHO Evaluation Strategy for COVID-19 Vaccines

Dr Deus Mubangizi, Unit Head of WHO Prequalification, discussed the process of vaccine pre-qualification and emergency use listing of the WHO. He explained that 73% of countries worldwide currently have regulatory systems that operate below WHO Global Benchmarking Tool Performance Maturity Level 3, which corresponds to a stable, well-functioning, and integrated regulatory system. They therefore rely on countries operating at Levels 3 and 4 to ensure drug product quality. WHO responded through the prequalification program to assess and identify products that are quality assured for procurement by UN, International, Regional and National procurement agencies for use by member states. The WHO prequalification program uses international standards and guidelines which ensure wide applicability across the globe. Regulation of drugs is a balancing act between promoting and protecting public health, by facilitating access to the market but yet, controlling the market to ensure that public health is not compromised. The WHO Emergency Use Listing (EUL) was

developed in response to the 2014-2016 Ebola outbreak and provides a risk-based approach to expedite availability of health products in emergency situations for a time-limited period (more details available from:

<https://www.who.int/teams/regulation-prequalification/eul/>).

Dr Mubangizi outlined the different features of prequalification and EUL and explained that EUL timelines for the abridged procedure are 1–2 months, compared to 2–4 months for full assessments. The WHO has published a number of documents regarding EUL procedures and criteria, including:

- Roadmap templates (e.g. <https://www.who.int/publications/m/item/roadmap-for-evaluation-of-astrazeneca-azd1222-vaccine-against-covid-19>),
- Target product profiles (see https://www.who.int/docs/default-source/blue-print/who-target-product-profiles-for-covid-19-vaccines.pdf?sfvrsn=1d5da7ca_5&download=true)
- Regulatory guidelines (<https://www.who.int/publications/m/item/considerations-for-the-assessment-of-covid-19-vaccines-for-listing-by-who>)
- EUL/PQ guidelines and expressions of interest criteria (https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/resources/1_EOI-Covid-19_Vaccines.pdf?ua=1)

Alignment is ongoing and Dr Mubangizi provided details of the roadmaps for assessment and in-country approval of COVID-19 vaccines, and the WHO working group position of labelling and package inserts for COVID-19 vaccines. It is a WHO led global assessment of vaccines with the involvement of regulators from all 6 WHO Regions and Stringent Regulatory Authorities. This ensures that the assessment is robust, representative and transparent thus facilitating trust and application of reliance approval measures at the national level, which is important for swift pandemic response. He provided an example of the Pfizer vaccine with expected dates of approval by EMA and EUL/PQ of late December 2020, and authorization in LMICs expected starting at the end of January 2021. Overall, prequalification has proven to be a valuable tool for the international response against COVID-19 pandemic, facilitating robust evaluation of health products and their access and approval at national level.

Assessing Safety in Pregnant Women Exposed to COVID-19 Vaccines After Emergency Use Approval in LMICs

Dr Narendra Kumar Arora from the INCLIN Trust International, introduced the unique challenges for monitoring maternal immunization safety in LMICs. In most LMICs registries and reporting systems are often inadequate, and complications of pregnancy or birth outcomes are not systematically counted or reported. Similarly, obstetricians and midwives may not be familiar with tracking AEFIs. India intends to vaccinate 300 million healthcare workers in the first stage of COVID-19 vaccine roll-out, approximately 10-15 million of whom are women of child-bearing age, therefore the risk of inadvertent vaccination during pregnancy is high. As mentioned throughout this webinar, harmonization of monitoring is key to prevent duplication of recording and to allow comparability of findings.

A recent study assessing the preparedness for introduction of new maternal vaccines (MIACSA project) showed delivery of maternal immunization services is mostly jointly organized between maternal, newborn, child and adolescent health (MNCAH) and expanded programs on immunization (EPI), with antenatal care facilities the primary point for administration in the majority of countries (<https://www.who.int/publications/i/item/maternal-immunization-and-an-antenatal-care-situation-analysis-report-of-the-miacsa-project-2016-2019>). One area for improvement is documentation of immunization of the pregnant woman, which would benefit from better standardization.

Regarding harmonization of data collection, the global vaccine safety multi-country collaboration has performed a prospective surveillance study assessing seven adverse maternal and neonatal outcomes across seven countries in Europe, Africa, the Middle East and India (<http://inclen-trust.org/inclen/global-vaccine-safety-multi-county-collaboration-project-safety-in-pregnancy-p-95/>). Utilizing harmonized case definitions developed by the Brighton Collaboration GAIA project, this study has helped to establish background rates of selected adverse pregnancy outcomes and has highlighted some of the ongoing challenges including the need for strong and sustained collaboration between programs, the need for improved documentation and training, and the development

of active and responsive surveillance systems for monitoring maternal and neonatal outcomes.

In India, a digitalized safety vigilance program is being prepared for passive AEFI reporting after roll-out of COVID-19 vaccine in the next few weeks. The reporting network has been expanded to include hospitals, medical colleges, and private practitioners, and AEFI committees have also been expanded to include medical specialists, cardiologists, neurologists, respiratory medicine specialists, and obstetricians. Overall, harmonization of monitoring systems, assessment of background rates, and amendment of monitoring systems to include relevant data from pregnant women will help provide transparency, which, together with effective communication, will help to maintain public trust in the vaccine.

Panel Discussion

The panel discussion was chaired by Prof Ruth Karron from the John Hopkins Bloomberg School of Public Health. Prof Karron provided a brief overview of the PREVENT guidance in the context of vaccination of pregnant women with COVID-19 vaccines, including assessment of the suitability of novel vaccine platforms, designing and planning of clinical trials which include pregnant women, and ensuring fair inclusion of pregnant women in vaccine delivery, unless the risks of vaccination outweigh the benefits.

A panel discussion then followed, with panelists:

Tracey Goodman, Team Lead, Life course & Integration Team, EPI Unit, Department of Immunization, Vaccines & Biologicals (IVB), World Health Organization (Geneva).

Jeffrey Roberts, Associate Director for Scientific Affairs, Office of Vaccines Research and Review, CBER/FDA

Emily Erbelding, Director, NIAID Division of Microbiology and Infectious Diseases

Geeta Swamy, Associate Professor, Dept ObGyn, Associate Vice President for Research, Duke University; Vice Dean for Scientific Integrity, Duke University School of Medicine

Prof (Dr) Narendra K Arora, Executive Director, The INCLIN Trust International, New Delhi, India

Key discussion points outlined below:

Existing data and future data collection

- More data in pregnant women are needed
- Goals, and consideration of pros and cons of initiation of specific studies in pregnant women (e.g. Phase 2 studies in pregnant women) or including this population in ongoing Phase 3 studies
- Data on risk of vaccination in the first trimester, including potential risk of pregnancy loss should be obtained as soon as possible
- Sequential assessment of endpoints in clinical trials (e.g. first establishing efficacy and then moving on to risk groups) may be less beneficial in the context of a pandemic response and groups at risk should be assessed in parallel to allow specific populations to receive the vaccines earlier
- After just two days of vaccination in the US, many pregnant women have already enrolled in V-safe, a smartphone-based tool supported by the US CDC to monitor safety in individuals receiving COVID-19 vaccines. Important that these data are analyzed to provide real time assessment of safety in pregnancy.
- Future trial design considerations – is it necessary to include a placebo group if the goal is to assess safety, as more data on vaccine safety can be obtained if all participants are vaccinated rather than if some receive placebo

COVID-19 vaccines in pregnant women

- Roll-out of novel vaccines to pregnant women should preferably not start until DART data are available when required by regulatory agencies. It is possible that some platforms may not require DART data if such data have previously been obtained from vaccines which use the same platforms
- The role of male partners and other family members in decision-making should be considered
- Consensus that 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 perspective
- 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,
- The consensus of the discussion was that lactating women should receive vaccines similar to the non-pregnant adult population

Key considerations for ensuring robust data collection

- Post-licensure/post-marketing safety surveillance should include designing studies which include pregnant women
- Registries are a key tool but recruitment is often difficult so there should be a focus on engaging healthcare providers to use them
- Large healthcare databases can be used for observational/prospective studies although challenges involve linking pregnancy, mother, and child data
- Inadvertent exposure during vaccination of healthcare workers provides a good opportunity to develop and implement a global initiative with a structured, comprehensive protocol to follow maternal and infant outcomes, and can help to tailor surveillance programs
- The importance of standardizing protocols and data collection tools for data collected by various stakeholders was emphasized
- It is important that existing EPI and MNCH systems and tools are used
- Strong recommendation that additional specialists including data scientists are included on EPI committees

Communication

- Need for effective communication to give confidence and allow pregnant 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
- Communication of AEFIs can be very complex, particularly when explaining indeterminant cause to lay persons
- 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 women and to manage expectations regarding AEFIs
- Stakeholders vary culturally, with family very much involved in decisions for pregnant women in some cultures

Q&A session: Risk/benefit assessment

- Risk/benefit assessment should also be based on absolute risk, as despite pregnancy being associated with severe COVID-19, the absolute risk is still low
- There are many factors to consider when assessing the potential risk. Factors include the local epidemiology and impact of the outbreak, occupation, types of exposures and assessment of risk for each, health status and comorbidities, age, contact with other people at risk, etc. These all need to be balanced with personal choice and what data is available regarding safety and efficacy of the vaccine, which now is not available for pregnant people specifically.

SUMMARY

Drs Sobanjo-ter Meulen and Munoz thanked everyone for attending and summarized the key takeaway messages from the webinar:

- Collaborative effort and co-ordination between stakeholders is essential
- 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

Webinar Data

Total number of registered attendees including speakers and organizers: 352

Total number of registered attendees excluding speakers and organizers: 332

Institutions attending: 150

*including funders, developers, regulators, universities and research centers

Developers attending: 46

List of attending developers

Advaccine
Ambrosino Biotech Consulting
Arcturus Therapeutics
AstraZeneca
Bavarian Nordic A/S
Beijing Institute of biological Products CO Ltd
Beijing Minhai Biotechnology Company
Beijing Stemexcel Technology Co Ltd
Biological E Ltd
Bionet
BravoVax
Butantan Institute
Cadila Healthcare Ltd
Cansino Biologics Inc
Clover Biopharma
Codagenix Inc
Curevac
Farmacologicos Veterinarios SAC
FBRI SRC VB Vector
Fiocruz
IAVI
Icosavax
Immuno-Vax LLC
Imperial College London
Inovio
International Vaccine Institute
Janssen
J&J
Latham Biopharm Group
Medigen Vaccine Biologics Corp
Merck
Novavax
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Themis biosciences
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Valneva
Vaxart
Vismederi
Walvax Biotech
Zydus