MEETING REPORT — 18 November 2021

COVAX: MATERNAL IMMUNIZATION WORKING GROUP WEBINAR

ADVANCES IN MATERNAL IMMUNIZATION SCIENCE AND IMPLEMENTATION IN TIMES OF COVID-19: HOW HAS THE COVID-19 PANDEMIC IMPACTED THE FUTURE OF MATERNAL IMMUNIZATION?

Co-chairs: Dr Ajoke Sobanjo-ter Meulen and Prof Flor M. Munoz

EXECUTIVE SUMMARY

On 18 November 2021, the COVAX Maternal Immunization Working Group (MIWG) held a webinar on Advances in maternal immunization science and implementation in times of COVID-19: how has the COVID-19 pandemic impacted the future of maternal immunization?

OVERVIEW: SESSION 1

Dr Ajoke Sobanjo-ter Meulen, co-chair of the COVAX MIWG, opened the meeting and provided a brief update on the ongoing challenges of vaccinating pregnant women, including the need to encourage uptake.

The keynote speaker, Dr Melanie Saville, Director of Vaccine Research at Coalition for Epidemic Preparedness Innovations (CEPI), provided an overview of CEPI's role in maternal immunization, supporting clinical trials, collaboration between key stakeholders, and the key role of the COVAX MIWG. She highlighted lessons that can be learned from the COVID-19 experience, and how improvements can be made for future campaigns against priority pathogens and disease "X".

In the first session of the webinar, four speakers presented data assessing the risk-benefit of COVID-19 vaccine using post-approval data. In the first talk, Dr Noa Dagan, Head of Data and AI-driven Medicine at Clalit Research Institute provided an overview of a vaccine effectiveness analysis of data in pregnant women in Israel. She highlighted the need for correct methodology and matched pairs in time, without inclusion of retrospective data. Data from the analysis showed vaccine effectiveness of 96% for documented infection and 97% for symptomatic infection, which are in line with those for the general population.

Dr Alisa Kachikis, Assistant Professor of Maternal-Fetal Medicine at the University of Washington, then provided an overview of available data on vaccine reactogenicity in the US and highlighted the importance of reactogenicity and safety data in overcoming vaccine hesitancy. In general, pregnant women have had lower rates of reactogenicity to COVID-19 mRNA vaccines than non-pregnant women, with the exception of injection site pain.

Prof Marian Knight, Professor of Maternal and Child Population Health at the University of Oxford and Head of the UK Obstetrics Surveillance System (UKOSS), then provided an overview of the UK's experience of tracking COVID-19 during pregnancy using UKOSS. The UKOSS system was established in 2005 and collects anonymous data on pregnancies across all obstetrics units in the UK. A recent analysis showed how the patterns of COVID-19 have changed with new variants, with unvaccinated pregnant and post-partum women now being disproportionately more severely affected by the delta variant compared with non-pregnant women of the same age. The UKOSS system is also being used to collect data on outcomes during the RECOVERY study, meaning that robust pregnant outcome data are being collected which can be rapidly integrated into treatment guidance.

Professor Cristiana Toscano, Head of the Collective Health Department at the Federal University of Goiás closed the first session with an update on the disease burden and vaccination experience in Brazil. She described the timeline of vaccination of pregnant women in Brazil, from high-risk only, through to recommendation for all, with a temporary stop following a death of a pregnant woman following vaccine receipt. Up to 15 November 2021, 35% of pregnant and post-partum women in Brazil were fully vaccinated against COVID-19, with low rates of (severe) adverse events.

OVERVIEW: SESSION 2

The second session of the webinar was a panel discussion, focusing on the de-risking of vaccine development for maternal immunization. Dr Alejandra Gurtman, Vice President of Vaccine Research and Development at Pfizer provided a brief overview of the Pfizer COVID-19 maternal immunization study, which is currently in the Phase 3 stage with last subject last visit anticipated for August 2022. Based on the current experience, Dr Gurtman highlighted a number of questions for future studies including decisions regarding studies in both high- and low- and middle-income (LMICs) countries, using existing data from the same vaccine platform, whether Phase 1 studies are needed in pregnancy, and the importance of identifying the optimum gestation period for vaccination.

The following points were highlighted in the discussion session:

- The broad scale of vaccination of pregnant women during the COVID-19 pandemic has raised the profile of maternal immunization, including in LMICs
- The success of mRNA vaccines in the COVID-19 pandemic has opened up the possibility for their use in other diseases, e.g. RSV or as combination vaccines
- Vaccine inequity remains a major issue. Market forces, together with vaccine nationalism, are the main drivers of this problem. Therefore equitable access to vaccines should be considered at the planning stage
- Exclusion of LMICs from clinical trials has resulted in a lack of data in these settings which may contribute to lag in recommendations
- While many pregnant women are able to access COVID-19 vaccines, uptake remains low. There is also a clear divide in vaccine uptake based on education, understanding of science, race, ethnicity, exposure to the media, political affiliation, and geography. Vaccine hesitancy remains a major issue. Drivers of vaccine hesitancy differ between LMICs and HICs; in LMICs, apathy is a key driver based on lack of disease burden data. The slow vaccine uptake among pregnant women could potentially have a major impact on any maternal immunization scheme
- Education of pregnant women and healthcare professionals, open communication, and engaging pregnant women in clinical development are key to enable access and reducing vaccine hesitancy among pregnant women. Changes in messaging early in the pandemic have also contributed to the reluctance of many women to be vaccinated

OVERVIEW: SESSION 3

The third session of the webinar focused on policy and regulatory considerations for the future. Prof Ruth Karron from the Department of International Health at John Hopkins Bloomberg School of Public Health discussed the PREVENT guidance recommendations for including the interests of pregnant women in development and delivery of vaccines. Whereas currently pregnant women are by default excluded from trials, PREVENT proposes the presumption of inclusion unless there are scientific and ethical reasons for exclusion. Prof Karron then provided details of the COVID-19 maternal immunization tracker (COMIT) which provides a global snapshot of policy recommendations for maternal COVID-19 vaccination over time.

Dr Marion Gruber provided an overview of the FDA pathway to vaccine approval and current national and international initiatives involving vaccines and therapies for pregnant women. In the current approach, DART data does not need to be collected pre-clinically, and can be performed as late as Phase 3 studies unless the vaccine is specifically indicated for use in pregnancy, which may delay access in an epidemic or pandemic situation. There has been a call for a paradigm shift towards inclusion of pregnant women in clinical trials, and the need for systematic plans to collect relevant safety and immunogenicity data early in clinical development. Dr Gruber concluded by providing some information on the FDA's related national and international initiatives.

In the final talk of session 3, Prof Linda Eckert, Professor of Obstetrics and Gynecology at the University of Washington provided an overview of her work in the ACOG Immunization, infectious disease, and public health preparedness work group. Despite recommendations by professional society recommendations to include pregnant women in COVID-19 trials, this did not occur.

She explained the efforts of the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal and Fetal Medicine (SMFM) in rapidly publishing and updating practice recommendations, and clarifying positioning regarding COVID-19 vaccination during pregnancy.

OVERVIEW: SESSION 4

The final session of the webinar was a roundtable discussion on pandemic preparedness and maternal immunization post-COVID-19. The session was chaired by Dr Denise Jamieson, Chair of the Department of Gynecology & Obstetrics at Emory University School of Medicine and panelists were Prof Cristiana Toscano, Prof Ruth Karron, Prof Linda Eckert, Professor Esperanca Sevene, Associate Professor of Clinical Pharmacology at the Eduardo Mondlane University, Mozambique, Dr Sami Gottlieb, Medical Officer at the WHO, and Dr Erik Karikari-Boateng, Head of the Center for Laboratory Services at the Ghana Food and Drug Authority.

The key outcomes from the discussion were:

Key data needs include:

- Early DART and clinical data in pregnant women
- Collection of background rates of maternal and infant outcomes, particularly in LMICs
- Disease burden data in LMICs – vaccine benefit-risk assessments cannot be performed without background data
- Vaccine effectiveness data, particularly for LMICs. Effectiveness studies should use standardized protocols and frameworks that allow for evaluation in different settings
- Safety data by vaccine platform, as much of the global safety data is for mRNA vaccines, which are not available in most LMICs

Types of surveillance systems which could be utilized:

- Expansion of pharmacovigilance studies which collect background maternal/infant outcomes and disease burden data
- Leverage existing systems for passive collection of necessary data (similar to the UKOSS)
- Obstetrics observatories could be used for mining available data sets

Communication to pregnant women and healthcare providers

- Divisions in uptake need to be addressed
- Form working groups to specifically target communication regarding maternal immunization
- Proactive recruitment of professional vaccination champions who live in the regions of people being vaccinated
- Prior to the start of the next pandemic, data and information should be shared to the general public, healthcare providers, and policy makers, rather than just the academic and scientific communities, so that there is already positive messaging about vaccination during pregnancy
- Proactive preparation of a clear message of the benefits of vaccines and medications during pregnancy
- Effective utilization of social media platforms
- Positivity of messaging (rather than e.g. lack of concerning safety signals)

Other key considerations

- Presumption of inclusion of pregnant women, rather than exclusion
- Proactive organization and initiation of systems is needed before the start of a pandemic
- Pregnant women are either at same risk or higher risk than other adults and so should be in vaccine campaigns

KEY FINDINGS AND OUTCOMES

In summary, the key takeaways from the meeting were:

1. The importance of every pregnancy and consideration of what pregnant women want to know about vaccination and how they want to be told
2. Leveraging of existing systems, networking, harmonizing, and standardizing methodologies in advance of a pandemic situation. This includes utilizing networks of expertise, having ready to go protocols, and pre-identified sites for studies
3. Use of new technology, including AI, to aid in modelling issues, social media messaging, and to more rapidly address the needs of pregnant women

MEETING SUMMARY

TIME (PT)	SESSION	SPEAKER
7:00 am	Workshop welcome Introduction of keynote speaker	Ajoke Sobanjo-ter Meulen Flor Munoz
7:05 am	**Keynote Lecture**	Melanie Saville
7:20 am	**Session 1 — Vaccine benefit-risk assessment post approval**	*Moderator*: Andy Stergachis
7:20 am	Vaccine effectiveness in pregnant women — Israel	Noa Dagan
7:30 am	Vaccine reactogenicity in pregnant women — US	Alisa Kachikis
7:40 am	The power of obstetric surveillance systems — the UK's experience tracking COVID-19 during pregnancy and the impacts of variants and vaccination	Marian Knight
7:50 am	COVID disease burden and vaccination strategies among pregnant women in Brazil	Cristiana Toscano
8:00 am	Questions & Answers	Andy Stergachis
8:10 am	**Session 2 — COVID-19 vaccines: De-risking of vaccine development for maternal immunization**	*Moderators:* Ajoke Sobanjo-ter Meulen & Flor Munoz
8:10 am	Introduction	Ajoke Sobanjo-ter Meulen
8:15 am	**Panel Discussion**	
	Panelists 1. Shabir Madhi 2. Janet Englund 3. Kathy Edwards 4. Alejandra Gurtman 5. Padmini Srikantiah	
9:10 am	**Session 3 — Policy and regulatory considerations: The way forward**	*Moderator*: Flor Munoz
9:10 am	Regulatory guidance/role (FDA) — how does COVID pandemic change the path for vaccine approval and access for pregnant women – Regulatory framework for maternal vaccines in the future	Marion Gruber
9:20 am	Obstetric professional societies role in supporting access of vaccines for pregnant women	Linda Eckert
9:30 am	COMIT and PREVENT, what we've learned about data-driven policy decisions, and what we should anticipate in the future?	Ruth Karron
9:40 am	Discussion	Flor Munoz
9:55 am	**Session 4 — Roundtable Discussion on Pandemic preparedness, Maternal immunization post COVID-19**	*Moderator*: Denise Jamieson *Curators*: Ajoke Sobanjo-ter Meulen & Flor Munoz
9:55 am	LMIC Post-approval vaccine evaluation	Christiana Toscano
	LMIC Regulatory and policy perspective	Mimi Darko Esperanza Sevene
	WHO Perspective	Tracy Goodman
	Vaccine Policy	Ruth Karron
	Vaccine Hesitancy	Linda Eckert
10:35 am	Wrap-up	Ajoke Sobanjo-ter Meulen Flor Munoz

WELCOME AND INTRODUCTION TO THE WEBINAR

Dr Ajoke Sobanjo-ter Meulen (co-chair of the COVAX Maternal Immunization Working Group) welcomed everyone to the webinar. She opened the discussions by highlighting that while access to COVID-19 vaccination has now been widely permitted for pregnant women, they remain an under-vaccinated group. In the US, only ~30% of pregnant women are vaccinated, which is considerably below general population levels [1]. At the same time, pregnant women with symptomatic COVID-19 have a 70% increased risk of death [2], and approximately 97% of pregnant women hospitalized or dying from COVID-19 are unvaccinated [3].

Pregnant women continue to be excluded from COVID-19 vaccine trials. However, the RECOVERY trial in the UK, which evaluates treatments that may be beneficial for COVID-19, has included pregnant women and has resulted in a change in clinical care for pregnant women with COVID-19 in the UK (https://www.recoverytrial.net). Vaccination against COVID-19 is considered the single most important intervention to prevent both maternal and fetal complications from COVID-19, and post-approval studies of the v-safe pregnancy registry have indicated no increased risk of miscarriage or other complications [4].

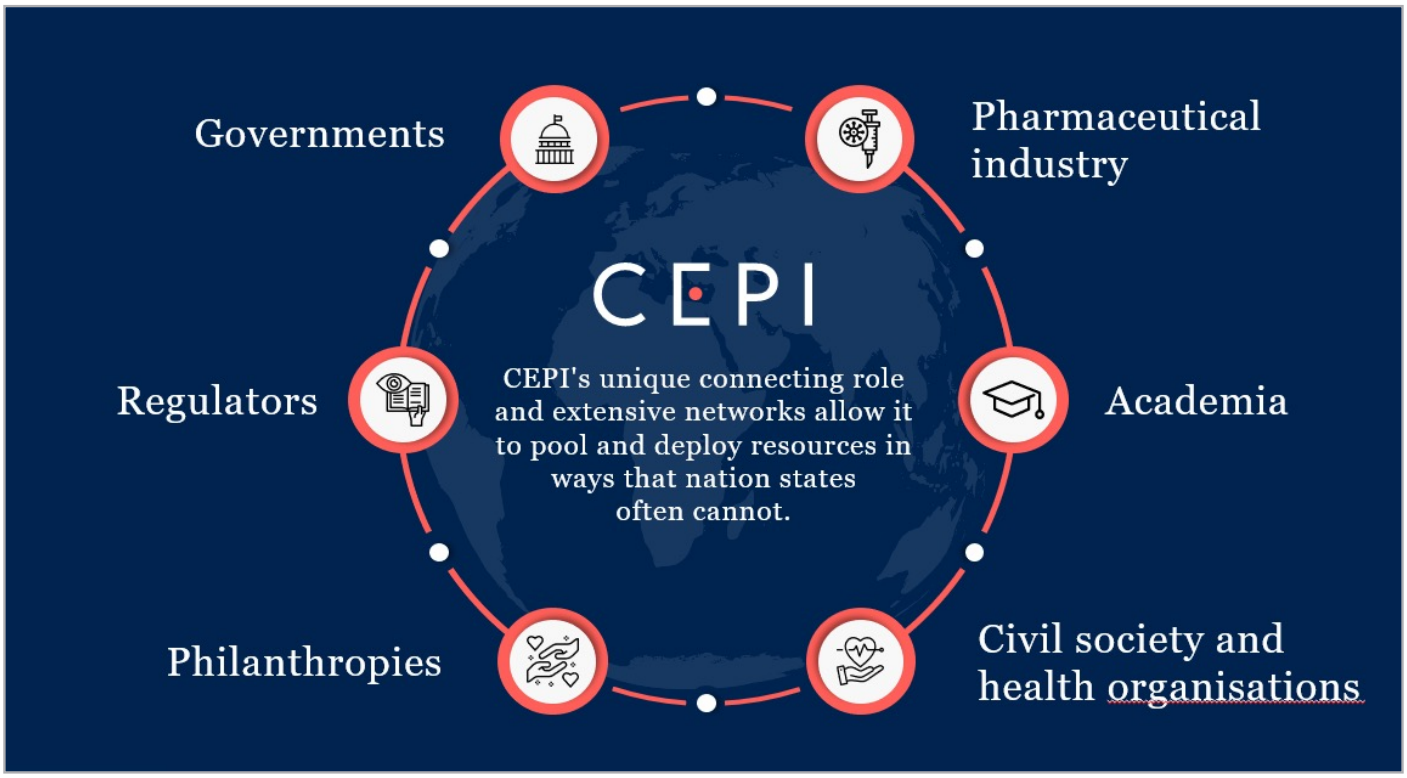
It is clear that we need to invest in linking obstetrics and vaccine data systems before any new pandemic, as well as enabling pregnancy surveillance data to be collected worldwide and inclusion of pregnancy women in vaccine clinical trials.

RESEARCH AND DEVELOPMENT APPROACHES TO MATERNAL IMMUNIZATION

In the keynote talk, Dr Melanie Saville, Director of Vaccine Research at Coalition for Epidemic Preparedness Innovations (CEPI) provided an overview of the vision and mission of CEPI, to accelerate the development of vaccines and other biologic countermeasures against epidemic and pandemic threats so they can be accessible to all people in need, resulting in a world in which epidemics and pandemics are no longer a threat to humanity. CEPI aims to achieve equity by working with multiple partnerships including industry, academia, governments, regulators, philanthropies, and civil society organizations to pool and deploy resources in a way that nation states often cannot.

In terms of maternal immunization, CEPI endorses the PREVENT guideline, which includes a number of R&D recommendations for developing vaccines that could be used by pregnant women in epidemic and pandemic situations [5]. This includes consideration of the choice of vaccine and planning for inclusion of pregnant women in the clinical development phases, including any necessary pre-clinical studies such as development and reproductive toxicology (DART) studies.

CEPI are focusing on a number of priority pathogens included in the WHO R&D blueprint list, such as Lassa. Outcomes for Lassa are particularly poor for pregnant women, therefore they should be a priority group for vaccination. A stakeholder workshop including regulators, R&D, and clinical investigators has facilitated planning for vaccine development and alignment for R&D plans going forward [6, 7]. CEPI also support consensus-building and knowledge-sharing for inclusion of pregnant women in COVID-19 vaccine trials, including the COVAX MIWG. CEPI have funded clinical trials for an Ebola vaccine in Uganda (NCT04028349) and Democratic Republic of Congo (NCT04152486) which include pregnant women, and a trial specifically designed for evaluating safety and immunogenicity in pregnant and lactating women in Rwanda (NCT045556526). As good quality safety data is critical for evaluation of vaccines, particularly in pregnant women, CEPI has partnered the Brighton Collaboration in the Safety Platform for Emergency vaccines project to ensure access to vaccine safety expertise, standards, and assessment tools, such as the Benefit-Risk Assessment of Vaccines by Technology (BRAVATO). The vaccine platform is one of the key elements for



vaccine safety, and the Brighton Collaboration have now developed templates to aid with assessment of benefit-risk, including those for pregnant women.

She then provided a summary of the important role of the COVAX MIWG during the COVID-19 pandemic, including expert discussions, information exchange, and how this can help vaccine developers during a pandemic situation. We are now in a position to look beyond COVID-19 to see how we can improve the future of maternal immunization against priority pathogens and "disease X". These improvements include leveraging learning from the COVID-19 experience, including being better prepared in terms of vaccine platform data and setting up knowledge sharing mechanisms. Disease-specific approaches are needed for priority pathogens, and maternal immunization should be included in pandemic preparedness strategies. As part of this CEPI is developing virus family vaccine libraries of potential future threats. She concluded by summarizing the important work of the COVAX MIWG, both in the COVID-19 pandemic and beyond, and that while substantial progress has been made, there are still unmet needs for ensuring equitable access including inclusion of pregnant women in clinical trials and safety surveillance infrastructure in low- and middle-income countries (LMICs).

SESSION 1: VACCINE BENEFIT-RISK ASSESSMENT POST-APPROVAL

VACCINE EFFECTIVENESS IN PREGNANT WOMEN IN ISRAEL

Dr Noa Dagan, Head of Data and AI-driven Medicine at Clalit Research Institute provided an overview of a vaccine effectiveness analysis of data in pregnant women in Israel. In Israel, vaccination of the general population with the Pfizer vaccine started on 20 December 2020 and recommendations for pregnant women shifted during the first months from permitting pregnant women to be vaccinated to a recommendation. The percentage of pregnant women vaccinated then gradually increased during the first few months of the campaign and now most pregnant women are vaccinated, as they were vaccinated prior to becoming pregnant.

Data from Clalit Health Services, the largest healthcare organization in Israel covering >50% of the population, were used for analysis of vaccine effectiveness. Dr Dagan highlighted the need for observational data to study vaccine effectiveness in pregnancy, as pregnant women were not included in phase 3 clinical trials and it is plausible that immune system changes during pregnancy may alter responses to mRNA vaccines. Additionally, confidence in vaccine effectiveness has been shown to be a strong predictor of vaccine acceptance among pregnant women. However, estimating effectiveness from observational trials is challenging as people who choose to be vaccinated differ from those who don't in many baseline characteristics including demographics, geographics, health status, socioeconomic status, and cautiousness and therefore already differ in their likelihood of infection, likelihood of seeking medical care, and prognostic factors for severe illness. For example, in Israel, the group with highest socioeconomic status had the highest rates of vaccination early in the campaign but also the lowest rates of infection prior to vaccination. Therefore it is difficult to identify a suitable "control" in observational studies. As the vaccination status is therefore not randomly distributed, all the confounder variables related to either vaccination or outcome have to be identified prior to analysis of vaccine effectiveness. For the current analysis, over 25 confounding variables were identified which needed to be controlled for and therefore the source database needed to contain all these data variables for an accurate estimate of vaccine effectiveness.

What kind of data are needed for evaluation of vaccine effectiveness?

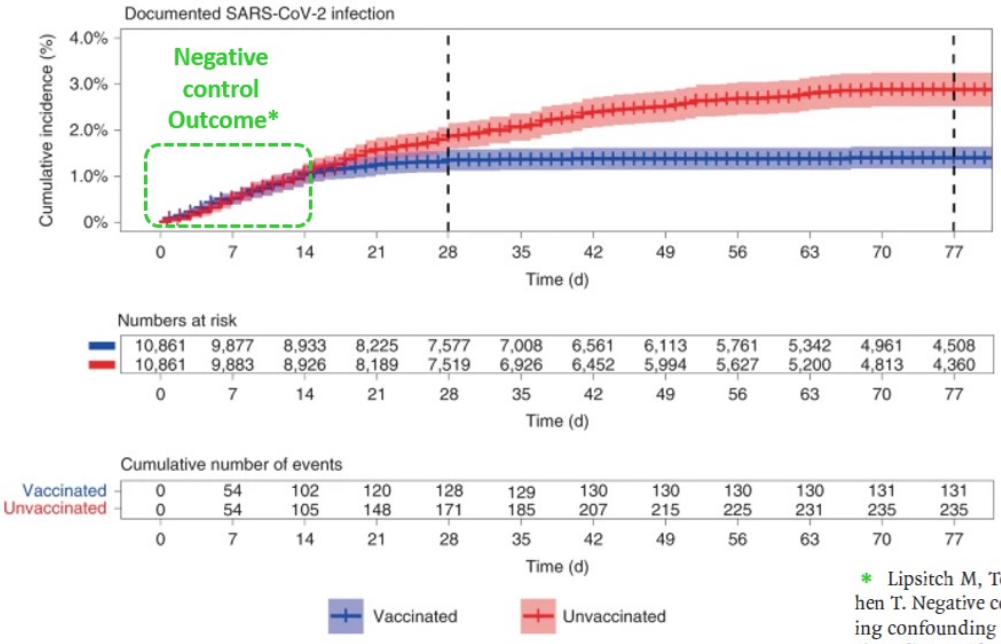
Anonymized data of a large cohort of individuals that includes:

- Vaccination status
- All laboratory COVID-19 PCR tests and results
- All outcomes for patients that are treated in the community
- All outcomes for patients that are treated in the hospitals (including hospitalization status, severity and death events)
- Relevant background sociodemographic information (age, SES, geographic area)
- Relevant background medical information (pregnancy trimester, all CDC risk factors for severe COVID-19, vaccination history etc.)

Dr Dagan explained why using a simple matching analysis was wrong, as the analysis is being retrospectively performed. The analysis should try to simulate a randomized clinical trial by identifying matched cases and controls for the same dates (e.g. when one person received the vaccine). It may be that controls get vaccinated in the future but it is important that this retrospective information does not influence their inclusion as a control at the time of "randomization" [8].

Dr Dagan then presented the results of the effectiveness analysis which was performed on 10,861 vaccinated pregnant women who were successfully matched with women who, on the same day, had not been vaccinated and had matching factors including age, trimester of pregnancy, living area, population sector, count of influenza vaccines in the last 5 years, and risk factors for severe COVID-19 [9]. The similarities in cumulative incidence of SARS-CoV-2 infection in the first 14 days of the study indicate that the vaccinated and controls were well matched [10], and a clear difference in incidence is evident from this timepoint onwards, indicating that the observed effectiveness is related to the vaccine. Vaccine effectiveness was estimated at 96% for documented infection and 97% for symptomatic infection. These estimates are in line with those for the general population therefore it is plausible that effectiveness in pregnant women can be estimated from that observed in the general population for future variants.

Fig. 1: Cumulative incidence of SARS-CoV-2 documented infection in vaccinated pregnant women and matched controls.



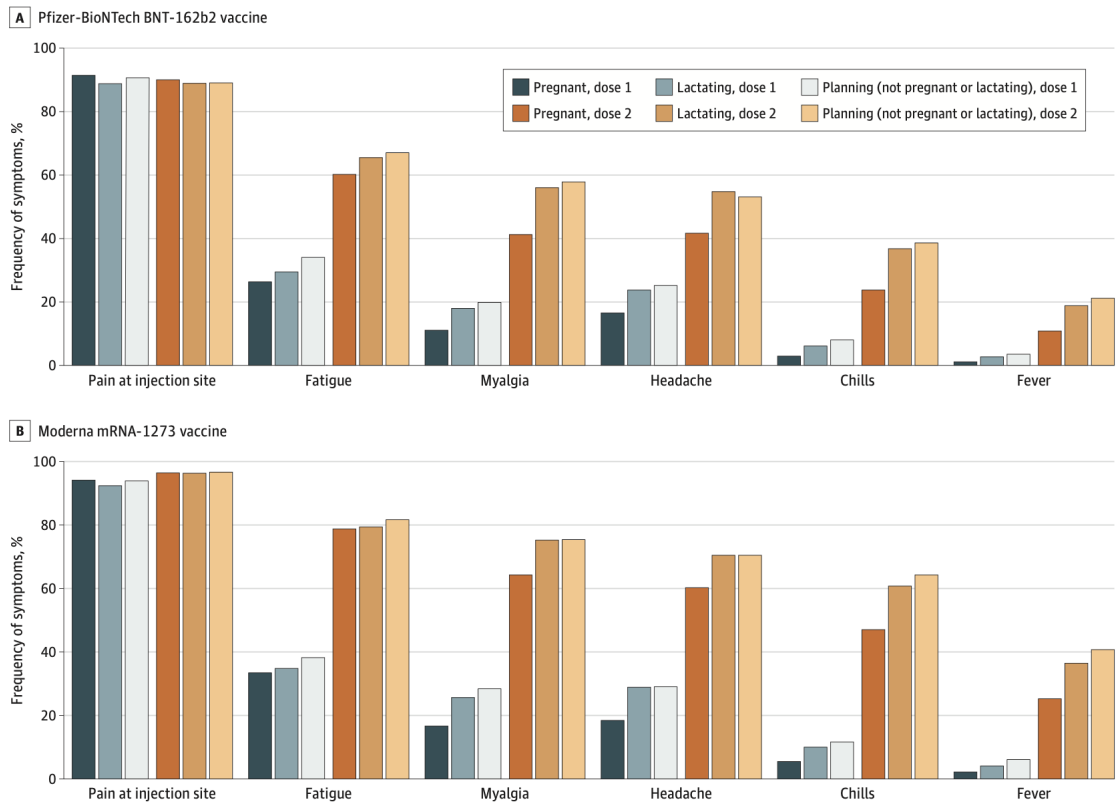
* Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology 2010;21:383-8.

As a final note, Dr Dagan noted the importance of good data infrastructure and the need for development of research capabilities for producing real-time data outcomes and analysis in future pandemics.

VACCINE REACTOGENICITY IN PREGNANT WOMEN IN THE USA

Dr Alisa Kachikis, Assistant Professor of Maternal-Fetal Medicine at the University of Washington, provided an overview of available data on vaccine reactogenicity in the US. She highlighted the importance of reactogenicity data on vaccine acceptance and hesitancy. At the start of the pandemic, there was very little information on the impact of COVID-19 in pregnancy. An important step occurred early in the pandemic, when surveillance systems were set up to monitor COVID-19 cases and outcomes, including CDC surveillance and establishment of national and regional registries. As stated previously, pregnant women were excluded from trials during COVID-19 vaccine development, despite high level advocacy from professional obstetrics organizations in the US, meaning that very little data were available when vaccines were initially rolled out. After rollout began, data on vaccine reactogenicity in pregnant women became available from CDC v-safe database, the Vaccine Adverse Event Reporting Surveillance (VAERS) system, and site-specific studies, e.g. University of Washington's Registry for COVID-19 vaccine in pregnancy and lactation.

Dr Kachikis then provided an overview of the results of the major US-based studies on reactogenicity of COVID-19 vaccines in pregnant women. In the main study published so far, which was based on data from the v-safe database and the VAERS system from 35,691 participants who reported pregnancy between 14 Dec 2020 and 28 Feb 2021 [4]. In general, pregnant women had lower rates of local and systemic reactogenicity than non-pregnant people from both dose 1 and 2 of the Pfizer and Moderna mRNA vaccines, with the exception of injection site pain. A second study on reactogenicity in pregnant and lactating women was performed as a prospective survey-based study by the University of Washington from 23 Jan to 16 March 2021, and included 17,525 participants with known pregnancy status, of whom 7,809 were pregnant, 6,815 were lactating, and 2,901 were planning a pregnancy in the near future. Similarly in this study, pregnant women tended to report fewer local and systemic reactions than either lactating or non-pregnant participants.



Analysis in lactating women showed low rates of interrupted breastfeeding (2.2–2.3%), and few participants experiencing decreased milk supply for less than 24 hours (5–7.2%), and concerned about that infant after vaccination (3.0–4.4%) across the 2 doses. Generally, concerns were women feeling worried about the vaccine in general, worry about breastmilk supply, and infant fussiness and sleepiness. After receiving the vaccine, the majority of participants in all 3 cohorts stated that they would recommend vaccination for their own specific cohort.

In summary, having data on the disease risk and safety and efficacy of vaccines is extremely important in a pandemic situation. Data collection can be facilitated by establishing networks for prospective clinical data collection together with surveillance systems. As a final note, it should also be remembered that pregnant women themselves may perceive their own risks from disease and vaccination very differently to policymakers and scientists, and many after often very willing to participate in research.

THE POWER OF OBSTETRIC SURVEILLANCE SYSTEMS: THE UK'S EXPERIENCE TRACKING COVID-19 DURING PREGNANCY AND THE IMPACTS OF VARIANTS AND VACCINATION

Prof Marian Knight, Professor of Maternal and Child Population Health at the University of Oxford and Head of the UK Obstetric Surveillance System (UKOSS), then provided an overview of the UK's experience of tracking COVID-19 during pregnancy. UKOSS was established in all obstetric units (194 hospitals) in the UK in 2005 and effectively covers the whole birth population of the UK. All hospitals provide a report monthly, including negative reports, and in the past rapid responsive studies have been conducted with other emerging infectious diseases such as influenza A/H1N1 and zika virus [11, 12]. The surveillance system collects anonymous data on women's characteristics, treatments, and outcomes, and the conditions included in the database change over time. To date, many studies have been completed including infectious diseases and many severe pregnancy morbidities, and the system can be used for continuing improvement in the quality of maternal care over time, and not solely for pandemic studies. A hibernated pandemic portfolio study was funded in 2012 after the A/H1N1 pandemic, as part of pandemic preparedness for any future pandemic. A number of activation tests were performed in the intervening years, including using seasonal influenza data, and the study was modified for assessment of SARS-CoV-2 in pregnant women and activated from 19 March 2020. A number of papers have been published based on data collected in the system, including a paper in the BMJ reporting data on the first 6 weeks of infection in pregnant women admitted to hospital with COVID-19 [13]. Most women had good outcomes, but one concern was the 8-fold higher rate of admission for black pregnant women compared with white women. Based on this finding, guidance was rapidly put in place in conjunction with the Royal College of Obstetrics and Gynecologists and Royal College of Midwives, to lower the threshold for consideration of hospital admission and escalation of care for women with black and minority ethnic backgrounds.

In the UK, pregnant women in extremely vulnerable groups became eligible for COVID-19 vaccination on 30 December 2020, with the majority eligible with non-pregnant people from their age group around spring 2021. From 1 March 2020 to 11 July 2021, 3371 pregnant women were admitted with symptomatic COVID-19. Of these women, 43% had a caesarean birth, 24% had pneumonia diagnosed, 21% required respiratory support, 10% were admitted to intensive care, and 0.4% died. Of the 3,036 babies born to these women, 21% were premature, 20% were admitted to a neonatal intensive care unit, and 1% were stillborn [14]. This pattern has changed significantly over time, with approximately 25% of pregnant women having the WHO composite indicator of moderate to severe infection during the period where wildtype SARS-CoV-2 was circulating, compared with 36% in the alpha variant-dominant period, and 45% with the delta variant. Their care requirements escalated during these 3 periods in a similar manner, and now with the delta variant, pregnant and post-partum women are disproportionately more severely affected compared with non-pregnant people of reproductive age [14].

Respiratory support needs during Wildtype, Alpha and Delta variant periods

UKOSS
UK Obstetric Surveillance System

	Wildtype N=1435 (%)	Alpha N=1765 (%)	Delta N=171 (%)	OR Alpha vs. Wildtype (95% CI)	aOR Alpha vs. Wildtype (95% CI)	OR Delta vs. Alpha (95% CI)	aOR Delta vs. Alpha (95% CI)
Composite indicator of moderate to severe infection	350 (24.4)	631 (35.8)	77 (45.0)	1.72 (1.48-2.01)	1.75 (1.48-2.06)	1.47 (1.07-2.02)	1.53 (1.07-2.17)
Evidence of pneumonia on imaging	274 (19.1)	486 (27.5)	63 (36.8)	1.61 (1.36-1.90)	1.65 (1.38-1.98)	1.54 (1.12-2.13)	1.64 (1.14-2.35)
Respiratory support required	183 (20.3)	466 (27.2)	52 (33.3)	1.47 (1.21-1.78)	1.39 (1.13-1.71)	1.34 (0.95-1.90)	1.43 (0.97-2.11)
Critical Care received	111 (7.7)	199 (11.3)	26 (15.2)	1.52 (1.19-1.94)	1.61 (1.24-2.10)	1.41 (0.91 -2.20)	1.60 (0.99-2.59)

Use of steroids has increased over time, although usage of pharmacological treatments for pregnant women admitted to hospital with COVID-19 remains low, with only 25% of pregnant women admitted to intensive care receiving steroids for maternal indication. Regarding perinatal outcomes, a 23% increase in neonatal unit admission was seen during the period where the alpha variant was predominant. Data for the delta variant are still coming in but there appears to be an increase in pre-term and late second trimester births. Of the pregnant women admitted to hospital or intensive care between 1 February and 30 September 2021 with symptomatic COVID-19, 98.1% and 98.7%, respectively, were unvaccinated. Additionally, maternal deaths have increased in the latest wave of infection, with 13 deaths from July to September 2021, at least 85% of which were unvaccinated women.

UKOSS is also being used to collect data on outcomes during the RECOVERY study, meaning that robust pregnant outcome data are being collected for all pregnant women included in the trial, and findings on beneficial treatments are being rapidly integrated into guidance for treatment of pregnant women with COVID-19.

In summary, obstetric surveillance systems such as UKOSS and those which have also been set up in LMICS, allow for rapid activation of COVID-19 studies. Results from UKOSS have shown that ethnicity, obesity, increasing maternal age, and comorbidities increase the risk of hospitalization and severity of COVID-19 in pregnant women, and the risks to pregnant women have increased with changing variants, although it is unclear whether this is due to severity of the changing variants or reluctance to use evidence-based medical therapies in pregnancy. Overall, the evidence points to the fact that vaccination is strongly protective against severe COVID-19 disease in pregnant women.

COVID-19 DISEASE BURDEN AND VACCINATION STRATEGIES AMONG PREGNANT WOMEN IN BRAZIL

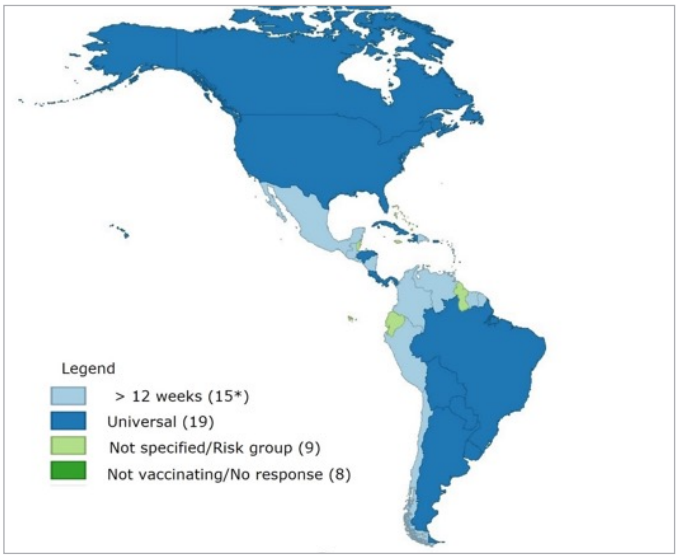
Professor Cristiana Toscano, Head of the Collective Health Department at the Federal University of Goiás in Brazil and member of the PAHO TAG and WHO SAGE working groups of COVID-19 vaccines then provided an overview of the burden of disease and vaccination experience in pregnant women in Brazil. In Brazil, COVID-19 vaccine rollout began on 17 Jan 2021 with CoronaVac and AstraZeneca COVID-19 vaccines. At this point, pregnant women were only considered for vaccination if they were considered in one of the priority or high-risk groups for vaccination for other reasons, but this advice changed in late April 2021 where vaccination was recommended for all pregnant women, based on disease burden evidence. As of mid-May 2021, cases and mortality from confirmed COVID-19 were very high in pregnant and recently pregnant women (276 and 21 per 100,000 inhabitants, respectively). A recently published study based on data from the SIVEP-Gripe national surveillance system included 945,460 cases of severe acute respiratory illness, of whom 50% had confirmed COVID-19. The study included 11,074 pregnant or recently pregnant women aged 10–49 years and showed that mortality was highest amongst pregnant women with COVID-19 who were aged 30–39 years or who had diabetes, hypertension, or other cardiovascular diseases, compared with other groups and other respiratory diseases [15]. Mortality was highest in areas where maternal mortality was already elevated. Previous data from an assessment of surveillance data in April 2021 also noted disproportionality high maternal mortality rates, particularly in the post-partum period, and similarly to the UK data, racial disparities in disease burden, ICU admission, and mortality rates [16].

In early May 2021, the death of a pregnant woman after receipt of a viral vector COVID-19 vaccine led to a suspension of COVID-19 vaccination until early July 2021, when advice for vaccination of pregnant women was based on risk-benefit analysis of risk from COVID-19 versus risk of thrombotic thrombocytopenia syndrome (TTS) from COVID-19 vaccination.

Professor Toscano provided information about the Brazilian Obstetric Observatory COVID-19 which is a public dashboard which provides interactive monitoring information and dynamic visualizations on COVID-19 in pregnant women (https://observatorioobstetrico.shinyapps.io/covid gesta puerp br/).

Up until 15 Nov 2021, 46% of pregnant and post-partum woman in Brazil have received one dose of COVID-19 vaccine, and 35% have received a second dose. The incidence of confirmed COVID-19 remains very high in pregnant women (~750 per 100,000) therefore there is a strong need for increased vaccine uptake. A study on CoronaVac in 19,838 pregnant women aged 18–49 years in Brazil demonstrated a vaccine efficacy of the two-dose regimen of 41% (95% confidence interval: 27–52%) against symptomatic COVID-19, 85% (60–95%) against severe COVID-19, and 75% (28–92%) in preventing progression to severe disease [17]. As of 16 Nov 2021, there is a low rate of adverse events (66.5 per 100,000) and severe adverse events (10.2 per 100,000) in pregnant women who have received COVID-19 vaccines. In total, 79 deaths have been confirmed; 70 are still under investigation and one has been confirmed as TTS.

In the PAHO Americas region, only 2 countries stated that they weren't recommending vaccination of pregnant women as of 15 Nov 2021. There is a variation in policies across countries recommending vaccination, with some recommending universal vaccination whereas others specifying after 9 or 12 weeks.



**Mexico and Suriname > 9 weeks; Chile > 16 weeks*
Source: Country reports to FPL-IM/PAHO. Data as of 15 November 2021/

PAHO has been providing support for countries to implement national and regional safety surveillance systems, with strengthening of passive and active surveillance, education, and communication networks.

Q&A

- **Regarding the methodology used to match digital twins in the Israeli data analysis, how could this be used in countries which do not have such comprehensive data sets, such as in LMICs?**

  To compare vaccine effectiveness, there needs to be a way to create two groups that are identical in all confounders and only vary by vaccination status. If data are not available for all confounders, any vaccine effectiveness estimates may be influenced by these variables and therefore estimates may not be true measures of the effect of vaccination alone.

  Some countries (e.g. India) use vaccine effectiveness data from countries where more comprehensive data are available and combine these with local disease burden data. However, given the differences between individuals even in very small areas within Israel and the importance of matching the exact time of the decision making about whether to be vaccinated, this may not take into account potential confounders. Simulation models and artificial intelligence could potentially be used to create digital twins for assessment of vaccine efficacy if the population characteristics are known.

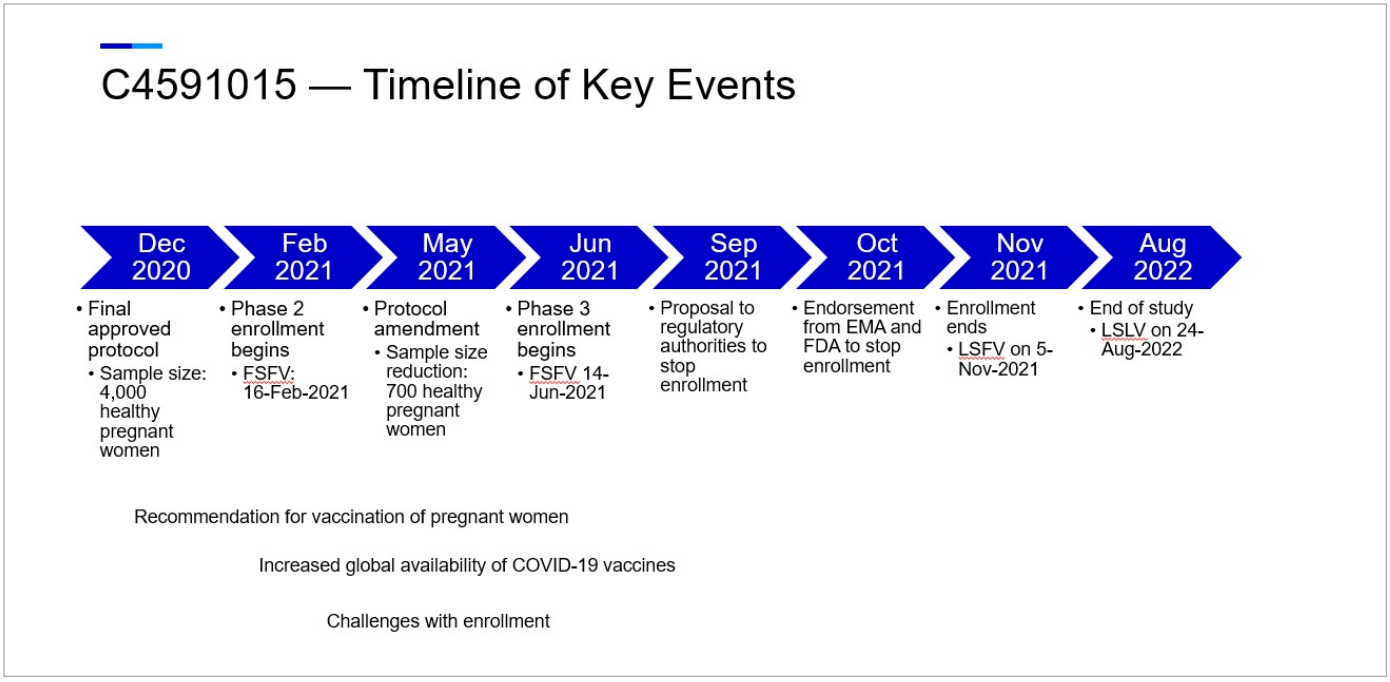
- **What advice do you have for planning observational studies assessing the real world effects of maternal immunization?**

  Firstly, limit the amount of data that is collected so that it isn't overwhelming. Secondly, build data collection in as part of a system that can be used outside a pandemic situation for collection of important data. Data should be collected passively as part of the standard of care for the patient as this will likely result in collecting all the data that is most relevant for analysis. The system should also be flexible to answer new questions and needs as they arise. Utilizing network contacts is also important for collaboration and sharing of data.

SESSION 2: COVID-19 VACCINES — DE-RISKING OF VACCINE DEVELOPMENT FOR MATERNAL IMMUNIZATION

PFIZER COVID-19 MATERNAL IMMUNIZATION STUDY AND REMAINING QUESTIONS FOR FUTURE STUDIES

To start the session, Dr Alejandra Gurtman, Vice President of Vaccine Research and Development at Pfizer provided a brief overview of the Pfizer COVID-19 maternal immunization study. Pfizer has been working on development of RSV and GBS vaccines for maternal immunization for several years and therefore were proactive in initiating potential studies of COVID-19 vaccines in pregnant women early in the pandemic. In April 2020, an initial interaction was made with CBER and a DART study was initiated in July 2020 which was accepted in Dec 2020. Within a few days, a finalized maternal immunization study was submitted to CBER primarily investigating safety and immune response in pregnant women and infants, with immunobridging to non-pregnant adult women. Efficacy was included as a secondary endpoint. Other analyses included antibody transfer to the newborn and infant antibody kinetics after delivery. The initial design was a phase 2 study where women were vaccinated between 24 and 34 weeks of gestation, with internal stopping rules and a crossover design to vaccinate placebo recipients within a month of delivery. Phase 2 enrollment began in the US in Feb 2021 as conducting a placebo-controlled study was difficult given the context of a recommendation for pregnant women to be vaccinated, the sample size was reduced from 4000 to 700 in May 2021. Phase 2 was completed with no evidence of safety signals. Phase 3 was initiated in mid June and enrolment stopped early in Nov 2021 due to recruitment challenges. Last subject last visit is anticipated for Aug 2022. Overall, 345 maternal participants (Phase 2: n=209, Phase 3: n=136) were enrolled in Brazil, South Africa, Spain, the UK, and the US. Mozambique was originally also included but the regulatory processes were longer than in other countries and the central ethics committee was concerned about the availability of the vaccine. 247 infants were born to maternal study participants by the end of Nov 2021.



The experience has highlighted severeal questions for consideration for future studies:

- How important is it to obtain an indication for pregnant women?
  - What is the medical value of an indication in pregnancy when the vaccine is recommended for all?
- Clinical trial initiation – how quickly can we really do it?
- Distinction on access after approval in high and LMICs
  - How critical is to include both settings in clinical trials?
  - How much do we need to anticipate logistics after approval (COVID vaccine shipment/storage in LIC countries)
  - Is it ethical to conduct a study in a country where the vaccine is unlikely to be approved/available?
- If we can move forward more quickly with the same platform (e.g. mRNA vaccines) and include pregnant women in other studies evaluating vaccines against different pathogens more easily
  - Will regulators agree that a DART study from a platform is sufficient or would it be an expectation to repeat the entire process for other mRNA vaccines?
  - Will a change in antigen delivery (LNPs) require additional DART studies?
- For other platforms, should we consider doing Phase 1 studies in pregnant women or is it enough to just allow them to be in phase 3?
  - How will adequate safety data be collected?
- How do we anticipate ideal time in gestation to administer new platforms?
  - How are we going to evaluate safety signals vs disease (e.g. Zika microcephaly)?
  - How early in pregnancy or in the clinical trial process can pregnant women be vaccinated?
- How important is to assess benefit from direct vaccination and protection to pregnant women and/or infant protection?

DISCUSSION

A panel discussion, moderated by Dr Ajoke Sobanjo-ter Meulen, then followed.

How has the use of mRNA COVID-19 vaccine in pregnancy shaped the Bill & Melinda Gates RSV vaccine strategy?

Dr Padmini Srikantiah, Deputy Director at the Bill & Melinda Gates Foundation then provided an overview of the Bill & Melinda Gates Foundation RSV strategy. RSV is the most common cause of lower respiratory tract infection in infants globally, with an estimated 18,000 deaths per year, almost entirely in LMICs and predominantly in infants <6 months of age. The Bill & Melinda Gates Foundation strategy focuses on prevention of deaths from RSV, for which two key approaches are being developed: maternal immunization and infant monoclonal antibody. To date, the pipeline is robust with several products in late stage development.

The broad scale of vaccination of pregnant women during the COVID-19 pandemic has raised the profile of maternal immunization, including in LMICs. Prior to the pandemic, mRNA vaccines were not part of the Foundation's RSV strategies, given the lack of safety data in any population. Their successful use during the pandemic, including in pregnant women, now opens

up the possibility of using these types of vaccines for prevention of RSV, and there is now an mRNA vaccine in clinical development.

There is also the potential for a pediatric vaccine targeting older infants or a combination vaccine targeting multiple respiratory pathogens. Initial combinations could be SARS-CoV-2 and influenza and/or RSV but one challenge would be whether the influenza component would need to be reformulated yearly and how easy that would be for an LMIC setting. Other challenges include whether efficacy would need to be demonstrated for each individual component first, and when the most appropriate gestational age would be for a combined vaccine. The concept of combination vaccines is still at an early stage and in the future the mRNA components could potentially also be rapidly modified in a pandemic situation, although several challenges as highlighted above still remain.

Learning from the COVID-19 pandemic: What do vaccine developers need to know to enable equitable access to vaccines for pregnant women in LMIC?

Prof Shabir Madhi, Professor of Vaccinology at the University of the Witwatersrand discussed the inequity of distribution of life-saving vaccines between high-income countries (HICs) and LMICs , which has been highlighted by the COVID-19 pandemic. The current experience echoes what has happened previously with other vaccines such as Haemophilus influenzae B vaccine, which took over 20 years to be introduced to the majority of LMICs and pneumococcal conjugate vaccine, which took 10 years to be introduced to LMICs. Similarly, in 2009, pandemic A/H1N1 vaccines only became available in LMICs after the pandemic had passed, rather than the pandemic.

The root cause of this is market forces, together with vaccine nationalism. To prevent this inequality in the future, access to vaccines should be considered in the planning stages, not just as an after-thought or once the needs of HICs have been met or over-subscribed. Another key force is the lack of government investment in research, healthcare services, and capacity for assessing of burden of disease in LMICs. In the absence of burden of disease data, vaccination becomes a lower priority for governments and it is harder for society to make the case as to why vaccines should be prioritized.

Industry can help reduce this inequality by generating necessary data from randomized clinical trials in LMICs. In the COVID-19 pandemic, only South Africa and one other LMIC country were included in phase 1 and 2 clinical trials. Not including LMICs in clinical development phases means there is a lack in understanding of how vaccines would work in those settings. This in turn may lead to a lag in recommendation for approval of vaccines for use in these settings (e.g. from the WHO), as it is not known whether the vaccines may perform differently in those settings.

He summarized that equity is not a simple issue to resolve, but trying to address the problem during a crisis is too late and these needs should be addressed in advance.

What has COVID-19 vaccine development taught us about maternal vaccine confidence and uptake in pregnant women?

Prof Janet Englund, Professor of Pediatrics at the University of Washington, highlighted that despite the clear evidence of the risks of COVID-19 during pregnancy, vaccine uptake in pregnant women is still low, even in countries where COVID-19 vaccines are freely available. There is also a clear divide in vaccine uptake based on education, understanding of science, race, ethnicity, exposure to the media, political affiliation, and geography. Despite research indicating that the vaccine is well-tolerated and results in antibody transfer to the infant and in breastmilk, there remains a large battle to overcome vaccine hesitancy which appears to be becoming more pronounced.

Prof Madhi confirmed that there is also a high level of vaccine hesitancy in South Africa. The drivers of low uptake in LMICs are seemingly slightly different to the drivers in HICs, and while they include hesitancy and mis-information, apathy is also a key driver based on the lack of availability of quality burden of disease data. This

results in few reports of cases and death rates, which then feeds into a narrative that COVID-19 is not an African problem and therefore society does not consider vaccines to be necessary. In some countries, like South Africa, vaccine hesitancy is now a much greater problem than access. Six months into the vaccination program, less than 30% of adults in South Africa have been vaccinated, which has led to poor decisions like extending vaccination to age groups who do not benefit much from vaccination rather than optimizing uptake in vulnerable age groups.

In Canada, a 25% lower COVID-19 vaccine uptake has also been observed compared with the general population and one major concern is how this is going to affect overall maternal vaccination programs in the future. It is likely that most women who enroll in the GBS and RSV vaccine trials will be highly educated, and are not from the demographics who may most benefit from the vaccine. There remains a huge issue of a lack of trust in science; vaccination has become politicized, which may substantially affect future vaccine programs. While maternal tetanus vaccine uptake is now nearing 100% in countries where it has been implemented, the misinformation surrounding COVID-19 vaccines poses a risk to other maternal immunization programs, and potentially more catastrophically, on childhood immunizations overall.

What can we do better to generate timely, accessible, and robust vaccine safety data in pregnant women prior to and during pandemics?

Prof Kathryn Edwards, Sarah Sell and Cornelius Vanderbilt Professor in the Department of Pediatrics at Vanderbilt University School of Medicine highlighted three key areas where improvements need to be focused: education of pregnant women and healthcare professionals, open communication, and engaging pregnant women in clinical development. Many pregnant healthcare workers understood the risks of COVID-19 during pregnancy and were very motivated to participate in safety studies. Education of providers is also key, with positive statements issued by professional bodies aiding in reducing hesitancy among pregnant women and healthcare providers. Open communication should also be prioritized, using the right people to convey the right messages, and utilizing technologies such as app-based systems which were rapidly embraced by pregnant vaccine recipients to carefully monitor the safety of vaccine in real time.

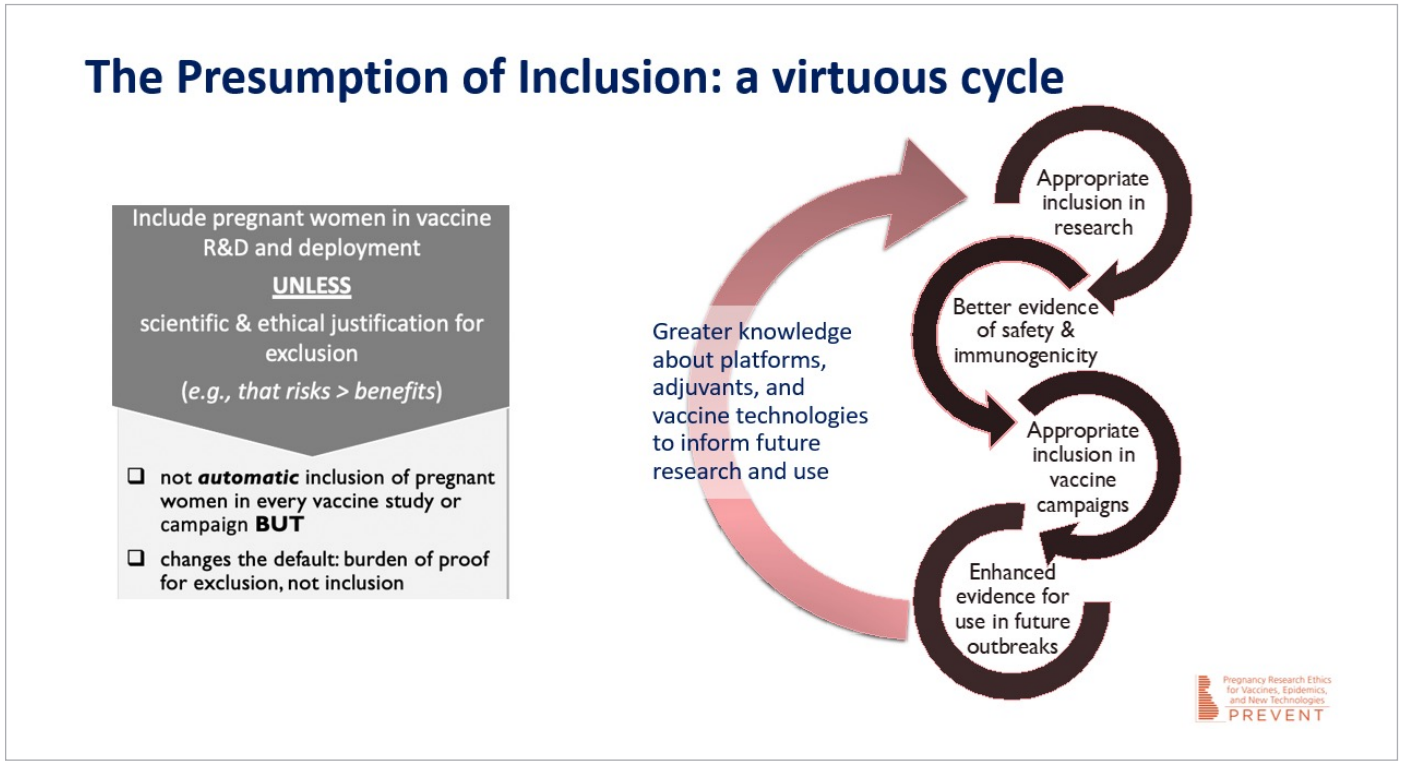
Dr Esperanca Sevene also provided some information about the Mozambique experience, where vaccine acceptance is very high in the general population. While vaccination of pregnant women has begun only recently driven by requests from gynecologists, acceptance is good but reduced by the previous contraindication in pregnancy, which has confused the message about the utility of COVID-19 vaccines in pregnancy.

COMMIT AND PREVENT: WHAT WE HAVE LEARNED ABOUT DATA-DRIVEN POLICY DECISIONS, AND WHAT WE SHOULD ANTICIPATE IN THE FUTURE

Prof Ruth Karron from the Department of International Health at John Hopkins Bloomberg School of Public Health began her talk with a call to action, stating that while we have developed frameworks to consider and plan for the needs of pregnant women in the context of infectious diseases, pregnant women will continued to be disadvantaged unless deliberate and concerted actions are taken by stakeholders including governments, regulators, vaccine developers, and supranational organizations.

The PREVENT guidance provides 22 recommendations across three domains (preparedness, R&D, and vaccine delivery) to equitably and responsibly include the interests of pregnant women and their offspring in the development and delivery of epidemic vaccines [5]. The presumption of exclusion, i.e. exclusion from research leading to a lack of evidence and thus exclusion from vaccine delivery is one of the key elements underlying inequity in vaccine access. PREVENT proposed the presumption of inclusion, where pregnant women are included in research and therefore data are available and women are included in appropriate vaccine campaigns. However, this doesn't mean that pregnant women should be included at all times, just that the default assumption should be inclusion rather than exclusion..

Of the 22 recommendations included, four have been particularly pertinent for the COVID-19 pandemic. Firstly, that pregnant women should not be left behind when new technologies are developed. Secondly, non-clinical studies required prior to clinical evaluation during pregnancy (e.g. DART studies) should be conducted early in clinical development, as promising



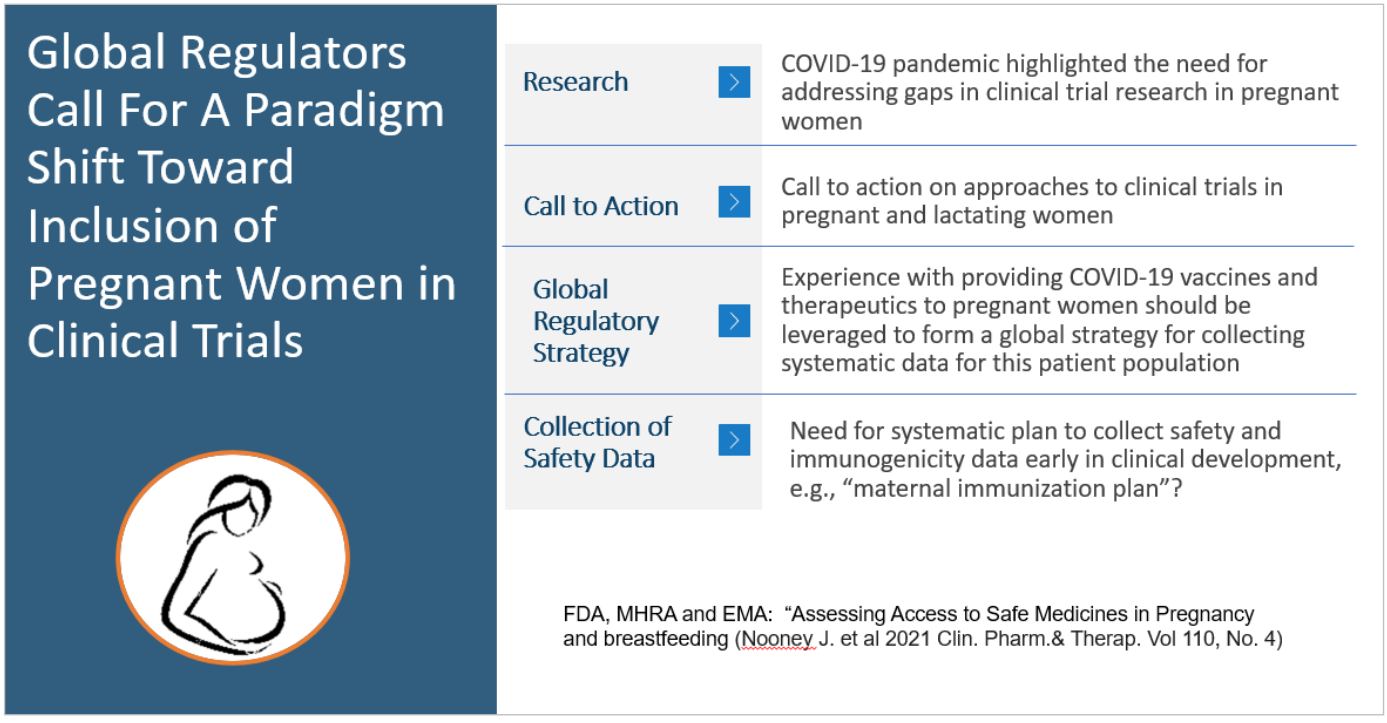
and appropriate candidates move to phase 2. Thirdly, pregnant women should have the opportunity to enroll in studies conducted during outbreaks when prospect of benefit > risk for pregnant women, their offspring, or both . Finally, pregnant women should be offered vaccines as part of an outbreak or epidemic response. Despite this recommendations being available at the beginning of the pandemic and inclusion of many high-risk groups in clinical trials, pregnant women were still left behind in COVID-19 vaccine development.

Prof Karron then provided details of the COVID-19 Maternal Immunization Tracker (COMIT) which is a global snapshot of public health policies that influence access to COVID-19 vaccines for pregnant and lactating women (www.comitglobal.org). The tracker shows the development of policy recommendations over time, and many countries have moved towards much more permissive recommendations over the last six months. However, many countries still do not recommend vaccination during pregnancy, and some do not have any policy at all, particularly in LMICs. The absence of DART, efficacy, and safety data delayed permissive recommendations in many countries. Additionally, as discussed early in the webinar, policy does not necessarily relate to uptake and changing recommendations have at least partially influenced the low uptake seen in pregnant women in many countries. Concerted change is needed towards the presumption of inclusion, otherwise inequities faced by pregnant women may increase in the future.

DID THE COVID-19 PANDEMIC CHANGE THE PATH FOR VACCINE APPROVAL AND ACCESS FOR PREGNANT WOMEN?

Dr Marion Gruber provided an overview of the FDA pathway to vaccine approval and current national and international initiatives involving vaccines and therapies for pregnant women. As discussed by the other presenters, she discussed the increased risk of severe COVID-19 in pregnant women and the exclusion of pregnant women from clinical development, with DART studies being the rate-limiting step.

The current approach to vaccine development involves local tolerance and repeat dose toxicity studies in pre-clinical research, followed by a move into the clinical



studies if the results are favorable. DART studies do not need to be conducted pre-clinically, and can be performed as late as Phase 3 studies unless the vaccine is specifically indicated for use in pregnancy. Therefore data on vaccine use in pregnancy are usually derived from post-authorization or post-marketing studies. In an ideal situation, DART studies should be included in pre-clinical development and as soon as favorable safety and immunogenicity data are available, phase 1 and 2 studies should be initiated in pregnant women, so that they can be included in phase 3 studies.

Over recent years, the FDA has engaged in a number of initiatives to address some of the unmet needs of pregnant women, including convening of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) in Nov 2015 to publicly discuss clinical trial considerations for vaccine use in pregnancy. Prof Karron provided the highlights of recent pregnancy and lactation activities in the US and Europe since 2016, including task force recommendations and guidance on studies in pregnant and lactating women. A meeting of the FDA in 2019 called for a paradigm shift towards inclusion of pregnant women in clinical trials, with a paper published in 2021 discussing access to safe medicines in pregnancy and lactation [18].

Dr Gruber concluded by providing some information on the FDA's national and international initiatives including the task force on research specific to pregnant and lactating women, which provides advice on therapies specific to pregnant and lactating women, the ICRMA workshop on pregnancy and lactation, which supports international collaboration for a global strategy for collecting data in pregnant women, and the working group pregnancy and lactation cluster, which aims to foster a global regulatory approach for medicines for use in pregnancy and lactation.

THE ROLE OF OBSTETRIC PROFESSIONAL SOCIETIES IN SUPPORTING ACCESS OF VACCINES FOR PREGNANT WOMEN

Prof Linda Eckert, Professor of Obstetrics and Gynecology at the University of Washington provided an overview of her work in the ACOG Immunization, infectious disease, and public health preparedness work group, which began in 2011 and is a group of ~12 obstetricians, gynecologists, and pediatricians with infectious disease training. The group was very active in the 2009 A/H1N1 pandemic, which is when cross-collaboration with the CDC was established and also resulted in a very productive collaboration during the Zika pandemic. These experiences, together with cross-collaboration with other groups, such as the Society for Maternal and Fetal Medicine (SMFM), meant that the group were very prepared when the COVID-19 pandemic struck. Within the group, there are many front-line providers and vaccine experts who are all supporters of maternal immunization.

OBSTETRIC PROFESSIONAL SOCIETIES CAN AND DO PLAY AN IMPORTANT ROLE IN SUPPORTING ACCESS OF VACCINES FOR PREGNANT WOMEN

- Established body of experts, experienced with maternal immunization, public health and infectious diseases, and familiar with roll of policy is critical
- Early engagement and cross collaboration across similar societies and pools of expertise
- Point persons for communication and organization critical
- Excellent opportunity for improving international discussion and advocacy

PROACTIVE PLANNING IS CRITICAL

Despite recommendations by professional society to include pregnant women in COVID-19 trials, this did not occur. ACOG and SMFM were very rapid in preparing joint statements highlighting the need for vaccines to be available for pregnant women, publishing these within days after authorization of the Pfizer vaccine [19]. These recommendations are regularly updated as new information becomes available, and ACOG has also published tools to aid members including conversation guides for clinicians, recommendations for vaccination sites, patient education resources, and billing information. As there was pushback from many vaccination sites not wanting to vaccinate pregnant women, ACOG, together with 17 partner organizations, published a statement further advocating for pregnant individuals to be free to make their own decision regarding their health and thus helping to keep access to vaccines for pregnant women.

When the WHO recommendations that vaccines should only be given to pregnant women at high-risk of exposure were published, ACOG and SMFM quickly responded reiterating the benefit to all pregnant women, to prevent confusion. Shortly after, the WHO revised their recommendation to be more permissive, which created a better global environment for access to COVID-19 vaccines for pregnant women. By mid-summer, when there was more data available on disease severity, vaccine safety, and antibody transfer, ACOG, SMFM and the CDC changed the recommendation from permissive to full recommendation that pregnant women receive the vaccines.

There is also ongoing advocacy by obstetrics societies behind the scenes and ACOG is now recruiting obstetric care provider volunteers to a vaccine confidence champion network to train healthcare providers on how to message and deal with vaccine hesitancy. Outside the US, obstetric societies in Canada and Brazil [20] have also been very active in promoting COVID-19 vaccination in pregnant women [21], and UpToDate also provide links to the ongoing efforts from professional societies all over the world.

Q&A SESSION

- **We had the example of the role of ACOG in promoting maternal immunization. What advice would you give to other professional obstetrics societies globally?**

  Ideally these societies should form a work group of experts who are more comfortable with maternal immunization than many healthcare providers are in general who can focus on providing messaging and promoting maternal immunization. Developing a cross-collaborative platform to share efforts globally would also be very beneficial

- **How do we overcome regulatory requirements hurdles for pregnant women to access vaccines?**

  Regulatory requirements are often seen as a hurdle but they are driven by underlying science. If sufficient data are available, then regulatory agencies are not a hurdle. However, other issues such as liabilitiy and ethics remain important

- **Is a specific indication for use in pregnancy needed?**

  Probably not, as prescribing info allow use in pregnant women within age categories if there are enough safety, immunogenicity, and efficacy data. However, it is important that pregnant women are included in clinical development so that these data are available

SESSION 4: ROUNDTABLE DISCUSSION ON PANDEMIC PREPAREDNESS AND MATERNAL IMMUNIZATION POST-COVID-19

Dr Denise Jamieson, Chair of the Department of Gynecology & Obstetrics at Emory University School of Medicine moderated the discussion session. Panelists for this session were Prof Cristiana Toscano, Prof Ruth Karron, Prof Linda Eckert, Professor Esperanca Sevene, Associate Professor of Clinical Pharmacology at the Eduardo Mondlane University, Mozambique, Dr Sami Gottlieb, Medical Officer at the WHO, and Dr Erik Karikari-Boateng, Head of the Center for Laboratory Services at the Ghana Food and Drug Authority.

1. **What is the present situation regarding COVID-19 vaccines in pregnancy in Ghana**

   As of six months ago, the lack of DART data meant that vaccination of pregnant women was not recommended in Ghana. Currently, with DART and real-world data available, there is the potential to vaccinate pregnant women, but the indication has to be specifically requested by the ministry and as yet vaccination is still not recommended

2. **What data are needed for the next pandemic and what types of surveillance systems (pre- and post-roll out) should be set up?**

   Earlier DART data and data from clinical trials in pregnant women are important. In terms of surveillance data, collection of background rates of maternal and infant outcomes is very important, particularly in LMICs where data are currently lacking. Studies which collect these data, such as the WHO pharmacovigilance study in pregnant women, should be expanded. Additionally, high level data, like that collected in the UK, can be leveraged in more settings to increase the baseline understanding and be 'activated' to answer specific questions during a pandemic. Post-vaccination analysis of data on mRNA vaccines from the US has been very important, but it would be nice to see similar systems set up in other countries to assess other vaccine types.

3. **What data are needed to characterize 1) the susceptibility and severity of disease in pregnancy and pregnancy outcomes, and 2) the safety and efficacy of potential interventions such as vaccines. How should these data be collected and how could the data collection and sharing be made more efficient?**

   Three key gaps which remain are strengthened surveillance systems for both pregnancy-related outcomes and vaccine adverse events, disease burden data, and vaccine safety and effectiveness estimates for LMICs. Obstetrics observatories could be used for mining available data sets, and frameworks for standardized data collection, analysis, and sharing should be set up. A WHO standardized pregnancy module exists for COVID-19 vaccine safety surveillance (https://www.who.int/publications/i/item/WHO-MHP-RPQ-PVG-2021.1). While not the ideal situation, having data available from other countries and settings are still very useful compared with no data, and could help guide early policymaking. We also need safety and effectiveness studies for different vaccine platforms, particularly for vaccines to be used in LMICs, with standardised protocols and frameworks. Where clinical trial data aren't available, information from other guidelines can be used to help guide decision-making. However, in the COVID-19 pandemic, major guidelines differed regarding recommendations for pregnant women. Additionally, the focus was on a risk-benefit assessment, which is hard to perform when no background disease data are available. A particular issue for LMICs was that much of the real-world safety evidence was collected for mRNA vaccines, which are not generally available to LMICs. Therefore a system which can collect data for other vaccine platforms is needed.

   It is paramount that as much as possible is organized before the start of a pandemic. In context of pandemic, pregnant women are either at same risk or higher risk than other adults and so should be in vaccine campaigns. An update to the GAIA paper discussing important parameters in maternal immunization studies should be updated and existing systems should be expanded to capture any data required. General pandemic-related data-collection platforms should also be integrated to incorporate collection of pertinent pregnancy questions within the same platform.

4. **What lessons learned from COVID-19 can be applied to future vaccines for pregnant women?**

   One key lesson is that the divide in uptake during pregnancy needs to be addressed, particularly in HICs. Uptake and acceptance of vaccination in pregnant women appears to be higher in LMICs (where available) than HICs. Proactive recruitment of professional vaccination champions who live in the regions of people being vaccinated is an important consideration. As the strength of provider recommendation is the most important factor, communication to these stakeholders as well as pregnant women themselves is very important. Prior to the start of the next pandemic, data and information should be shared to the general public, healthcare providers, and policy makers, rather than just the academic and scientific communities, so that there is already positive messaging about vaccination during pregnancy.

5. **How can we improve communication around maternal vaccination to improve maternal acceptance? (e.g. when to share information, what type of information, by whom?) Is knowing results from preclinical studies (e.g. DART) reassuring/sufficient for OB providers and vaccinators when deciding about vaccination of pregnant women?**

   A key element of this is to start preparing for next pandemic now, as it is harder to project a clear message in the middle of a crisis. Pregnant women and healthcare providers should be educated on the benefits of both vaccines and other medications in pregnancy, and it should not be the default case that they are scared to administer anything to a pregnant woman. Secondly, preparation in advance will help develop a clear message, as changing recommendations during a pandemic leads to confusion and increases hesitancy. Different audiences should be catered for in communication plans, with clear and consistent messaging and the effective use of social media platforms. One acknowledged difficulty is countering negative messaging e.g. regarding infertility. To counter this, information packages should be created in advance for common questions regarding components, vaccine platforms etc. Additionally, messaging should be improved to provide positive statements rather than the lack of safety signals.

6. **What lessons learned from COVID-19 can be applied to future pandemics in terms of protecting pregnant persons; what else should we do now to prepare for the next pandemic?**

   Lessons learned include non-optional inclusion of pregnant women in clinical development, moving collection of DART data earlier to before phase 1, and the importance of advanced planning and having surveillance systems already in place (e.g. hibernated systems which can be activated). Additional suggestions included randomized cluster trial of proactive social media messaging and studies on how to overcome provider biases in vaccine recommendations.

MEETING CLOSE

Dr Sobanjo-ter Meulen thanked all the speakers and attendees and highlighted the three important themes to come out of the meeting.

Three key takeaways:

1. The importance of every pregnancy and consideration of what pregnant women need to know about vaccination and how they want to be told
2. Leveraging of existing systems, networking, harmonizing, and standardizing methodologies in advance of a pandemic situation. This includes utilizing networks of expertise, having ready to go protocols, and pre-identified sites for studies
3. Use of new technology, including AI, to aid in modelling issues, social media messaging, and to more rapidly address the needs of pregnant women

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