MEETING REPORT — 8-9 November 2022

MATERNAL IMMUNIZATION WORKING GROUP MEETING REPORT

Co-chairs: Dr Ros Hollingworth and Prof Flor M. Muñoz

EXECUTIVE SUMMARY

On 8 and 9 November 2022, the Maternal Immunization Working Group (MIWG) held an in-person and online hybrid meeting. The objectives of the meeting were to provide an opportunity to share new data regarding maternal immunization, to discuss the landscape of vaccines under development for use in pregnant woman, and to consider how new vaccines, such as RSV and GBS, will be integrated into immunization programs for pregnant woman.

OVERVIEW: DAY 1

OPENING LECTURE: PRIORITIES FOR MATERNAL IMMUNIZATION AFTER THE PANDEMIC

Prof Flor Muñoz, Associate Professor of Pediatrics and Infectious Disease at Baylor College of Medicine, US gave the opening lecture which highlighted a number of lessons learned from the COVID-19 experience for enabling access to vaccines for pregnant women, including the need to proactively collect data on background maternal outcomes and to have safety surveillance systems already in place, prior to the next outbreak or pandemic. She provided an overview of clinical development of maternal vaccines, including those in late-stage development against Group B Streptococcus (GBS) disease and respiratory syncytial virus (RSV), as well as highlighting other diseases which are also being researched as potential areas for maternal vaccine development.

SESSION 1: THE IMPACT OF COVID-19 ON PREGNANCY

The first session concentrated on the experience of vaccinating pregnant women during the COVID-19 experience, and how this can be used to improve preparedness for future outbreaks and pandemics.

Dr Mercedes Bonet, Medical Officer in the Maternal and Perinatal Health Team at the World Health Organization (WHO), began the session by summarizing the global burden of COVID-19 in pregnant women and the variations in recommendations for vaccination worldwide. Pregnant women are at increased risk of severe disease and have been prioritized in many vaccine roll-outs worldwide. Ten vaccines, including mRNA, protein-based, and adenovector-based vaccines, have now been recommended by the WHO for use in pregnant women. In addition, the WHO recommends that pregnancy or breast-feeding should not be a barrier to COVID-19 vaccination. Vaccine recommendations continue to vary worldwide, with most countries recommending vaccination. However, 11 countries do not recommend vaccination for any pregnant women. The WHO has now developed a manual for vaccine safety surveillance, which contains a specific module on vaccination during pregnancy: https://www.who.int/publications/i/item/9789240032781.

Dr Richard Beigi, President of UPMC Magee-Women's Hospital provided an overview of ACOG's role in developing guidance for pregnant women about COVID-19 disease and the risks and benefits of vaccination. Throughout the COVID-19 vaccine development and roll-out phases, ACOG have strived for the inclusion of pregnant women in recommendations for vaccination and remain committed to addressing misinformation and updating guidance based on the ever-evolving pandemic situation.

Dr Dana Meaney-Delman, Chief of Infant Outcomes Monitoring, Research, and Prevention, and Dr Kara Polen, Associate Director of Communications in the Division of Birth Defects and Infant Disorders at the CDC provided an overview of maternal COVID-19 vaccination policy in the US, and the lessons learned from the pandemic experience. Data for the V-safe pregnancy registry has been a key tool in safety surveillance of COVID-19 vaccines in pregnant women and has provided considerable data on the effect of vaccination on maternal and infant outcomes. Of the main lessons learned from the pandemic experience, one important issue is to redress the balance between perceived theoretical risks of vaccination and actual disease risks when considering vaccination of pregnant women. The pandemic also highlighted the need to counter the spread of misinformation, engage healthcare workers, and rapidly obtain safety data to counter vaccine hesitancy.

The first panel discussion of Day 1 then followed.

Panel Discussion 1

Topics of discussion included the issues created by excluding pregnant women from initial COVID-19 vaccine research and development, vaccine recommendations for pregnant women, whether boosters should be given, and the potential for co-administration or combination of multiple vaccines during pregnancy to increase uptake.

The main findings were:

- Exclusion of pregnant women from research was a missed opportunity and led to delays in access to vaccines for this population when it became evident early in the pandemic that pregnancy was a risk factor for severe disease.
- Small scale safety studies could have been performed in parallel when it was evident that there were no serious safety concerns of vaccines being evaluated in non-pregnant adults.
- The view of risk should be changed from focusing on the theoretical risk of a vaccine to evidence-based risk:benefit evaluations, including the risk of disease.
- ACOG, CDC, and SAGE were proactive early in the pandemic because it became evident that pregnant women were at an increased risk of complications from COVID-19, as had been the case with previous respiratory virus outbreaks. Early guidance stating that pregnant women should be able to access vaccines was based on risk:benefit assessments, with V-safe data being key in switching this advice to a recommendation.
- In general, vaccination for pregnant women against COVID-19 should follow the guidance for the general population, including for booster vaccination.
- Vaccine fatigue is a major issue as vaccines do not give long-lasting immunity and do not keep pace with changing virus variants. This has resulted in many people being reluctant to have any further vaccinations.
- The number of vaccines offered during pregnancy should be considered, as many women may be reluctant to have multiple vaccines once new vaccines become available. Co-administration and possible combination vaccines should be evaluated.

SESSION 2: EVALUATING SAFETY AND EFFECTIVENESS OF VACCINES FOR PREGNANT WOMEN

Dr Pierre Buekens, Director of the Center for Emerging Reproductive and Perinatal Epidemiology at Tulane University started the second session of the day by demonstrating the Safe in Pregnancy (safeinpregnancy.org) living systematic review dashboard. The dashboard collates data from studies evaluating COVID-19 vaccines in pregnant women, and as of 8th November 2022 contained 121 studies including approximately 885,000 pregnant women. Data from all individual studies are included in the dashboard, and can be filtered by various parameters including region, publication date, and outcomes measured. In addition, the dashboard links to a meta-analysis of a small subset of studies which adjusted for potential confounders.

Dr Natasha Halasa, Professor of Pediatrics at Vanderbilt University Medical Center and Dr Samantha Olson, Epidemiologist at the CDC provided an overview of the results from a study performed by

the Overcoming COVID-19 Network, evaluating the impact of maternal COVID-19 vaccination on disease in infants <6 months of age. The study included 537 case infants (hospitalized for COVID-19) and 512 controls, with a median age of 2 months. Maternal vaccination prevented >50% of hospitalized COVID-19 cases in infants, with higher vaccine effectiveness in infants born to women vaccinated in the second half of pregnancy (>20 weeks gestation). Overcoming COVID-19 is continuing to collect data on infants with severe COVID-19, with the aim of filling current knowledge gaps including the effect of booster status, timing of maternal vaccination, and vaccine effectiveness by infant age.

Dr Katerina Rok Song, Research Scientist at the International Vaccine Institute, provided an overview of the ongoing clinical trial evaluating the safety and immunogenicity of a hepatitis E (HEV) vaccine in pregnant women. The vaccine is licensed in China and Pakistan but is not recommended for use during pregnancy. Dr Song described an upcoming phase 2 evaluating the safety and immunogenicity of the vaccine in pregnant and non-pregnant women which is planned to begin in January 2023. The placebo-controlled study will enroll approximately 2200 pregnant women and 150 non-pregnant women, with results expected in Q2 of 2025.

The second panel discussion of Day 1 then followed.

Panel Discussion 2

The second panel discussion was moderated by Prof Flor Muñoz. Panelists were Dr Pierre Buekens, Dr Natasha Halasa, Dr Samantha Olson, Dr Katerina Rok Son, Dr Leila Sahni from Baylor College of Medicine, Dr Andy Stergachis from the University of Washington, and Dr Nicky Klein from Kaiser Permanente Vaccine Study Center. Topics included effectiveness of COVID-19 vaccination in pregnant women, safety surveillance and specific challenges for LMICs, challenges associated with the HEV vaccine study, and vaccine fatigue.

The main findings were:

- COVID-19 vaccination during pregnancy is as effective as in non-pregnant individuals.
- COVID-19 vaccination protects women from hospitalization and in particular from severe outcomes and ICU admission.
- Safety surveillance in LMICs should leverage existing networks and collaboration with epidemiology and maternal health teams is needed to utilize data and data systems already in place.
- Vaccine effectiveness in LMICs is likely different to that seen in HICs owing to populations differences and lower rates of transplacental antibody transfer. Specific efficacy studies should be performed in LMICs to gain insight into the differences.
- Matched design studies are more informative for evaluating vaccine effectiveness than ones comparing outcomes to past data.
- One major challenge faced by the HEV vaccine study was the need to perform the study in a high-risk area. HEV is generally associated with extreme poverty, and data on pregnancy outcomes is very lacking in these populations, and no surveillance systems are in place.
- Consideration of the potential timings of maternal vaccination and age of infants being protected is especially important for seasonal diseases (e.g., influenza, RSV).
- It is likely that vaccine fatigue experienced during the COVID-19 pandemic will spill across to other vaccines. As observed in the US, rates of uptake of maternal vaccination appear to be lower than previous years, but this may change as the influenza season progresses.

OVERVIEW: DAY 2

Day 2 of the workshop focused on upcoming vaccines for pregnant women

SESSION 1: EVALUATING THE SAFETY AND EFFECTIVENESS OF FUTURE VACCINES FOR PREGNANT WOMEN

Dr William Gruber, Senior Vice President of Vaccine Clinical Research and Development at Pfizer started the day with an update on maternal GBS vaccine development. The Pfizer hexavalent GBS vaccine is currently being evaluated in a phase 1/2 clinical study in pregnant women, with results showing antibody responses across all serotypes, with similar responses to those seen in non-pregnant women and no advantage of aluminum adjuvant in terms of antibody levels in seen in infant cord blood. It is likely the vaccine is highly efficacious, but results are still to be confirmed. The vaccine is also currently being evaluated in a co-administration study in non-pregnant adults.

Dr Concepción de Alba Romero, a pediatric doctor and member of the Neonatal Infectious Diseases Committee in Spain then provided an overview of the impact of the COVID-19 pandemic on rates of GBS sepsis in Spain. Spain has seen a substantial reduction in the number of cases of early-onset sepsis since the introduction of intrapartum antibiotic prophylaxis (IAP), with the exception of 2020 when cases rose. This rise was in conjunction with high rates of false negative screens from home-based screening and mothers arriving too late to hospital for IAP. She concluded that a GBS vaccine is a necessary development that can help save lives of infants.

Professor Asma Khalil, Professor of Obstetrics and Maternal Fetal Medicine at St George's Hospital, London, UK then outlined the challenges of using an mpox (monkeypox) vaccine in pregnant women, and guidance from published articles on the prevention and management of mpox during pregnancy. While mpox is generally a mild, self-limiting disease, it can be more serious in immunocompromised individuals, including pregnant women. None of the available treatments are licensed for use in pregnancy, but some could potentially be used in high-risk situations (e.g. tecovirimat). A live, non-replicating vaccine (MVA-BN) could also potentially be used in pregnancy although is not licensed. As with COVID-19, pregnant women are being excluded from clinical trials in line with regulatory guidance.

Prof Chrissie Jones, Associate Professor in Paediatric Infectious Diseases at the University of Southampton, UK provided an update on the work of the Immunizing pregnant woman and infants network (IMPRINT). IMPRINT's aims include building an international network of stakeholders who were experts on maternal and neonatal vaccination, to increase awareness and uptake of vaccination, engage with industry via placements for trainees, to provide start-up funding to address prioritize challenges, and to fund post-doc fellowships in LMICs. Membership of IMPRINT is free: www.imprint-network.co.uk/membership.

In the final talk of session 1, Dr Gerald Voss, consultant project leader at the Coalition for Preparedness Innovations (CEPI) discussed CEPI's vaccine portfolio and strategic objectives. CEPI's strategic objectives are based on 3 pillars: Prepare, Transform, and Connect, which aim to develop vaccines and biologics against the most prominent known threats, increase preparedness against Disease X, and to connect stakeholders to enable rapid countermeasure development, effective response and equitable access for those in need. CEPI aims to be able to respond to the outbreak of a novel pathogen with a vaccine within 100 days, which will require significant front-loading of preparedness activities. As part of this preparedness, CEPI aims for timely inclusion of pregnant women in development and implementation of vaccines, as well as creation of a blueprint for expedited evaluation of vaccines during pregnancy. Dr Voss then gave an example of CEPI's support in maternal immunization against Ebola through funding of the INGABO phase 3 study.

A question-and-answer session then followed.

The following questions were discussed:

1. **Who should be vaccinated against GBS once a vaccine is available?**

   All pregnant women should be vaccinated, as screening is not 100% effective, IAP has not impacted LOD, and colonization can be variable over time.

2. **Is it possible to have a vaccine ready within 100 days?**

While this was not possible for COVID-19 vaccine development, which was achieved within approximately 9 months, a number of lessons can be learned from this experience which could help with meeting a 100-day target. Firstly, identification of potential pandemic pathogens and development of vaccine components based on related pathogens (e.g., as was done for COVID-19 with MERS and SARS-CoV spike proteins) could cut timelines for vaccine development once the pathogen emerges. As part of this, virus families could be characterized and stored, with one example per family moved into clinical trials to provide data in advance of emergence of a related pathogen. Additionally, the inclusion of pregnant women in these clinical trials would provide vital data in advance, enabling access to initial vaccine roll-out during an outbreak. Secondly, if immunogenicity data can be used for developing vaccines based on variant strains, timelines could be substantially reduced compared with the need for randomized clinical trials. However, manufacturers also would need to commit to production of vaccines before clear data are available, and therefore would need to potentially manufacture with considerable financial risk. Thirdly, having safety data readily available on vaccine platforms would allow vaccines to be swiftly developed with the emergence of novel pathogens, rather than needing to perform all safety evaluations from scratch.

3. **What are the other potential uses of GBS vaccine, apart from protection against neonatal GBS disease?**

   In the US, GBS is the leading cause of meningitis in under 18s, therefore a GBS vaccine could be beneficial in reducing the rate of meningitis in older children as well as neonates. In addition, use of a GBS vaccine could provide further insight on the role of GBS in pre-term labor and stillbirth, and potentially reduce these outcomes.

4. **What are the remaining legal challenges to allowing pregnant women to be part of vaccine research?**

   A lot has changed over recent years, with many of the legal hurdles removed for inclusion of pregnant women in vaccine research. One hurdle which remains is the perception of the theoretical risk of vaccine-related adverse events. Therefore, funding should be allocated to research the potential for these adverse events in general, so that these trials and candidate vaccines are more accessible to women during pregnancy.

SESSION 2: OPTIONS FOR RSV PREVENTION IN INFANTS

The final session of the meeting focused on vaccines and biologics for prevention of RSV in infants.

Dr William Gruber, Senior Vice President of Vaccine Clinical Research and Development at Pfizer opened the session with an overview of the data from the clinical development of Pfizer's RSVpreF vaccine in pregnant women. Following on from positive results in pre-clinical and phase 1/2 studies, the vaccine was evaluated in a phase 2b proof of concept study in pregnant women at 24–36 weeks gestation, showing high antibody responses and no safety concerns in women or infants. Exploratory estimates of efficacy were 84.7% (95% CI: 21.5–97.6%) against medically-attended lower respiratory tract infections (LRTIs) in infants and 91.5% (-5.6–99.8%) against severe LRTIs. The Matisse phase 3 study is being performed in 18 countries worldwide and includes approximately 7500 mother and infant pairs randomized 1:1 to 120 µ RSVpreF or placebo. Interim analysis estimated a vaccine efficacy against severe medically-attended LRTI of 81.8% (99.5% CI: 40.6–96.3%) in the first 90 days of life and 69.4% (44.3–84.1%) in the first 6 months. Against medically-attended LRTIs, efficacy was 57.1% (14.7–79.8%) and 51.3% (29.4–66.8%), respectively. These estimates met the pre-specified regulatory success criteria for severe medically-attended LRTI indicating clinically meaningful efficacy.

Prof Shabir Madhi, Dean and Professor of Vaccinology at the University of Witwatersrand, South Africa, then provided an overview of data from the Prepare trial, a global study evaluating Novavax's alum-adjuvanted F-protein nanoparticle RSV vaccine in pregnant women and their infants. While the study did not meet its primary endpoint of efficacy against medically-significant symptomatic LRTI through 90 days, exploratory analysis on the population of participants in South Africa showed vaccine efficacy ranging from 45% for medically-significant LRTI to 70% for RSV LRTI with severe hypoxemia through to Day 180. Furthermore, substantial reductions were seen in 'all cause' medically-significant LRTI, LRTI hospitalization, and LRTI with severe hypoxemia through to six months of age. Notably only 25, 28 and 32 women would need to be vaccinated to prevent a single episode of all-cause MS-LRTI, LRTTI hospitalization and LRTI with severe hypoxemia, respectively, indicating a substantial public health benefit of vaccination.

Dr Octavio Ramilo, Chief of the Division of Infectious Diseases at Nationwide Children's Hospital then concluded the presentations with an update on the use of monoclonal antibodies for prevention of RSV. He began by discussing the rationale for passive immunization against RSV rather than active immunization of young infants, based on data from antibody titers following maternal vaccination and transcriptome analysis of immune responses in young infants. Dr Ramilo then briefly described the history of anti-RSV monoclonal antibody development and provided a summary of the key data from clinical trials of nirsevimab and clesrovimab. Both monoclonal antibodies appear to provide high rates of efficacy against medically-attended LRTI, with higher antibody titers from nirsevimab than are seen after natural infection. He concluded by discussing the potential for resistance mutations, with evidence to date suggesting the risk remains small.

Two panel discussions then followed.

Panel Discussion 1

Panel discussion 1 covered lessons learned from conducting clinical trials in pregnant women and was moderated by Dr Janet White, Portfolio and Platform Lead at the Bill and Melinda Gates Foundation. Panelists included Dr William Gruber, Dr Chrissie Jones, Prof Asma Khalil, Dr Octavio Ramilo, Dr Katerina Song, Dr Gerald Voss, Prof Shabir Madhi, Dr Karen Bok, from the National Institute of Allergy and Infectious Diseases (NIAID), and Prof Kirsty Le Doare, Professor of Vaccinology and Immunology at St George's University, London. Topics discussed included preparedness for overcoming regulatory concerns for future pandemics, building and strengthening capacity for conducting clinical trials in LMICs, coadministration of vaccines in pregnancies, and the use of monoclonal antibodies vs maternal immunization against RSV.

The main findings from the first panel discussion were:

- In addition to regulators, sponsors and manufacturers need to be comfortable with performing research in pregnant women. Ideally, toxicology studies and phase 1 studies in non-pregnant adults need to be ready to go as soon as possible so that a study in pregnant women can be planned. DART studies can potentially be performed pre-clinically, although manufacturers may be reluctant to do this for every potential candidate due to financial risk.
- As seen in the COVID-19 pandemic, there was still a study set-up time of up to 6 months for clinical trials and this should be considerably shortened by proactive planning.
- Set up and conduct of the clinical trials in LMICs are easier if sites already have experience of conducting clinical trials, particularly during pregnancy.
- Obstetricians should be recruited, in addition to pediatricians, for vaccines which include a component of maternal protection. Mentoring of personnel running trials is important, as there is a limited number of experts in LMICs.
- Challenges to conducting trials during pregnancy in LMICs include the potential for outbreaks of other diseases or political unrest, both of which would reduce healthcare system capacity.
- As it is potentially a sensitive topic, strong community engagement may also be needed to increase acceptability and aid in recruitment of pregnant women to clinical trials. Within certain cultures it may not just be the pregnant woman herself who is deciding on whether to participate in a trial but would include other family/society members who also need to be engaged.
- One particular challenge for maternal immunization studies may be the lack of routine ultrasounds and inaccuracy of gestational age estimates, making it difficult to identify prematurity and the gestational window for vaccination.
- In the Africa region, regulators are becoming more willing to share information across authorities, with the possibility of performing collective reviews of the evidence. In addition, the WHO maturity levels are a good tool in strengthening regulatory procedures in LMICs.
- As highlighted during evaluations of COVID-19 vaccines, if specific data are not collected during trials, it is difficult to refute links to vaccination (e.g., changes in menstrual patterns). Collecting these types of data routinely in clinical trials may help in public acceptability, as any potential links to vaccination can be robustly evaluated. Cohort matching can also be used to help identify any differences in rates of events, particularly events that are population specific.
- There are a growing number of vaccines which can be administered during pregnancy, and the need for multiple routine vaccines may not be very acceptable to pregnant women, particularly if they do not understand the potential disease threat to themselves or their infant. Ideally, combination vaccines and coadministration should be evaluated, as well as the potential for priming of non-pregnant women where antibody titers can be maintained above protective thresholds for multiple decades.
- From the clinical data available to date, both monoclonal antibodies and maternal vaccination against RSV are efficacious. In LMICs, choice of treatments may be mostly driven by availability and cost, whereas in HICs monoclonal antibodies may be preferred in certain situations e.g., pre-term birth. Potentially, monoclonal antibodies would not be needed outside the RSV season whereas maternal immunization would be best administered all year round to ease implementation.

Efficacy estimates for vaccines may well differ once a vaccine is implemented outside of a clinical trial, therefore study populations should be ideally as close to real-world populations as possible. For example, in South Africa, approximately 50% of women were ineligible for inclusion in randomized controlled trials due to HIV status or obesity. Estimates for monoclonal antibody efficacy are expected to be more robust as the study populations were more representative of the real-world population. Studies evaluating the post-introduction impact of vaccines are also important to conduct.

- The lower rates of transplacental antibody transfer in South Africa compared with HICs observed in the RSV vaccine study were similar to those seen in a GBS vaccine study. Independently of HIV infection, hypergammaglobulinemia was noted as a risk factor for reduced transplacental antibody transfer. There is a high prevalence of CMV infection in South Africa, so this may result in a high prevalence of hypergammaglobulinemia. This also highlights the importance of trials at a local level which include representative study populations, and the awareness of any differences with other populations.

Panel Discussion 2

Panel discussion 2 then followed, discussing what needs to be done for the implementation of RSV vaccines for pregnant women in LMICs. The panel was moderated by Dr Ros Hollingsworth and panelists were Dr Bill Gruber, Prof Kirsty Le Doare, Dr Danny Feikin from the Departments of Immunizations, Vaccines, and Biologicals at the World Health Organization, Dr Niranjan Bhat Lead of the Vaccine Impact Research Team at PATH, Dr Jessica Fleming Maternal Immunization Delivery Lead at PATH, Dr Azucena Bradaji from the Barcelona Institute of Global Health, and Prof Esperança Sevene, Associate Professor at the Universidade Eduardo Mondlane Faculty of Medicine, Mozambique.

The main findings of the second panel discussion were:

- RSV is not perceived as a priority for vaccination compared with many other diseases. There is therefore a need to raise awareness of the burden of RSV and highlight the benefits of vaccination at a country-wide level. This should include evaluation of the full public health value of vaccines (e.g., against all-cause pneumonia) and evidence beyond phase 3 studies
- There should be a focus on implementation of vaccination, rather than just on pharmacovigilance. Pilot programs or randomized vaccine roll-out could aid in identifying issues with implementation and for more robust estimates of vaccine effectiveness in special populations or different geographical regions (e.g., endemic for malaria). In addition, practical points need to be considered, such as alignment with existing antenatal care and timings of visits. This can also help with vaccine delivery planning, e.g., number of doses per vial.
- LMICs face lots of competing priorities for disease management at a country level, so policy makers and clinical leaders need to have a clear view of the disease burden and potential public health benefits of vaccination.
- An absence of data negatively impacts vaccine uptake, therefore proactive collection of some of these outcomes (e.g., impacts on menstrual cycle) is needed so that these can be readily refuted with evidence.
- Public messaging and education of healthcare providers should be framed to highlight the overall public health benefits. Qualitative studies can also be performed to help understand the best communication strategies for engagement.
- In LMICs, pharmacovigilance is mostly based on spontaneous reporting, therefore under-reporting is an issue. Overall, there is a need for effective, specialized surveillance systems (e.g., integrated surveillance across respiratory diseases) to gain a clear insight on disease burden and allow robust estimates of vaccine effectiveness.

KEY MESSAGES AND TAKEAWAYS

In summary, the key takeaways from the meeting were:

1. Maternal immunization is a key public health strategy to improve maternal and infant health and reduce early life mortality worldwide.
2. Pregnant women with COVID-19 were quickly shown to be at increased risk of severe illness and death compared with non-pregnant women. Additionally, COVID-19 during pregnancy was also swiftly shown to be associated with increased risk for adverse pregnancy outcomes, such as preterm birth and stillbirth. However, recommendations for use of COVID-19 vaccines in pregnancy lagged behind those for the general population, primarily due to exclusion of pregnant women from clinical development programs for these vaccines.
3. The experience and successes of vaccination during the COVID-19 pandemic provide a tremendous and unique opportunity for maternal immunization efforts to continue in the post-pandemic era. Given the ongoing development of new vaccines for use in pregnant women to address other significant threats, such as Respiratory Syncytial Virus and Group B Streptococcus, it is important to learn from the COVID-19 vaccine experience, to ensure these vaccines can be implemented safely, effectively, and promptly, globally.
4. Vaccines produced with mRNA technology have the potential to increase the options for safe and effective vaccines against more pathogens, including combination vaccines, and allow improved options for the protection of women during pregnancy and infants in early life.
5. The lessons learned from the pandemic regarding research, development and implementation of vaccines in pregnancy can be applied to the next generation of vaccines for use in pregnant women.

This meeting provided an opportunity to highlight the hard work and commitment of the Maternal Immunization Working Group throughout the recent COVID-19 pandemic to enable the evaluation and utilization of COVID-19 vaccines in pregnant and lactating women. This working group will be maintained and expanded to address the threat of endemic-, epidemic- and pandemic-related morbidity and mortality by ensuring that pregnant and lactating women have timely and equitable access to safe and effective vaccines.

MEETING SUMMARY: DAY 1

TIME (PT)	SESSION	SPEAKER
10:00 am	Meeting Welcome and Introduction	Ros Hollingsworth Keith Klugman
10:15 am	**Opening Lecture:** Priorities for maternal immunization after the pandemic	Flor Muñoz
10:45 am	**Session 1**	*Moderator*: Ros Hollingsworth
10:45 am	Burden of disease and vaccine policy – a global perspective	Mercedes Bonet Semenas
11:05 am	Vaccine recommendations and role of professional societies	Richard Beigi
11:25 am	Considerations for supporting recommendations for vaccination during pregnancy and safety surveillance systems	Dana Meaney-Delman and Kara Polen
11:45 am	**Panel Discussion 1**	
	Panelists 1. Mercedes Bonet Semenas 2. Dana Meaney-Delman 3. Richard Beigi 4. Geeta Swamy	*Moderator:* Shabir Madhi
12:15 pm	Lunch Break (30 min)	
12:45 pm	**Session 2**	*Moderator*: Flor Muñoz
12:45 pm	Safe in Pregnancy & the Living Systematic Review	Pierre Buekens
1:05 pm	Overcoming COVID project: COVID-19 Vaccine Effectiveness	Natasha Halasa and Samantha Olson
1:25 pm	Evaluating the safety and immunogenicity of hepatitis E vaccine in pregnant women	Katerina Song
1:45 pm	**Panel Discussion 2**	
	Panelists: 1. Pierre Buekens 2. Natasha Halasa 3. Sam Olson 4. Katerina Song 5. Leila Sahni 6. Andy Stergachis 7. Nicky Klein	Moderator: Flor Muñoz
2:15 pm	Day 1 Close and concluding remarks	Ros Hollingsworth

WELCOME AND INTRODUCTION

After a brief introduction by Dr Ros Hollingworth, co-chair of the MIWG, Dr Keith Klugman (Director, Pneumonia, Bill & Melinda Gates Foundation) at the Bill and Melinda Gates Foundation opened Day 1 of the meeting with a brief discussion of the opportunities for maternal immunization that have arisen during the COVID-19 pandemic. While the reductions in child mortality seen in past decades experienced a setback during the pandemic, the positive changes towards vaccination developed during the pandemic provide a tremendous opportunity for maternal immunization post-pandemic.

Currently, approximately 50% of mortality in under 5s occurs in the first month of life. Currently available vaccines targeting young infants (e.g., pneumococcal conjugate vaccine [PCV] and rotavirus vaccines) primarily focus on reducing mortality from 3 months of age. However, candidate maternal RSV and GBS vaccines have the potential to reduce mortality from even earlier ages, including in the first month of life, and GBS vaccines could also help to reduce prenatal mortality.

Maternal vaccines still face many more barriers than vaccines targeting other populations. However, the de-risking of mRNA vaccines during the COVID-19 pandemic is a large step forward and may pave the way for a new generation of highly effective monovalent and combination vaccines, based on mRNA technology. In light of the experience during the COVID-19 pandemic, the two main objectives for this meeting were:

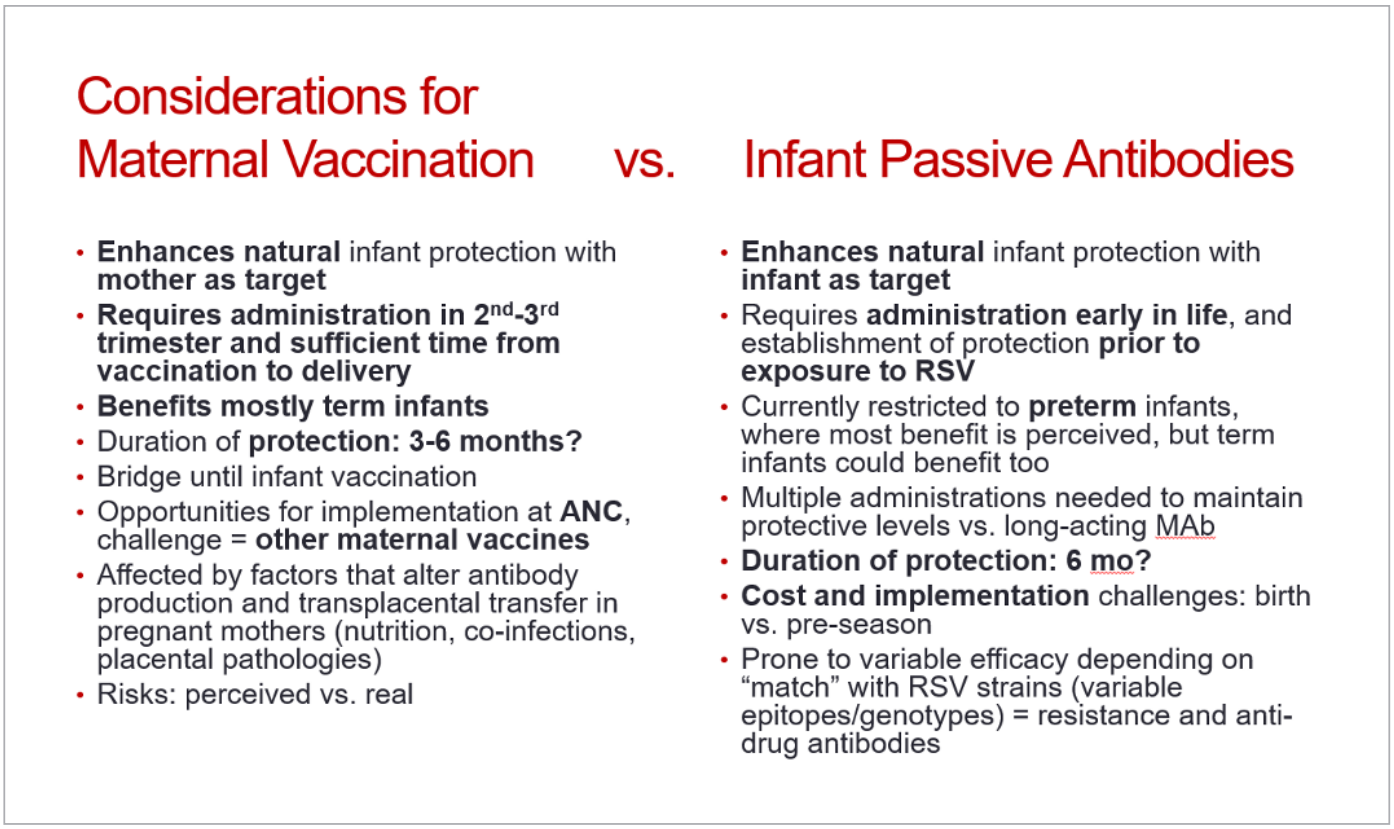
- To reflect on the successes and failures in maternal immunization during the COVID-19 pandemic
- To evaluate how the lessons learned from the pandemic can be applied to the next generation of vaccines for use in pregnant women

OPENING LECTURE: PRIORITIES FOR MATERNAL IMMUNIZATION AFTER THE PANDEMIC

Prof Flor Muñoz, Associate Professor of Pediatrics and Infectious Disease at Baylor College of Medicine, US, highlighted the priorities for maternal immunization in the post-COVID-19 pandemic era. The UN Sustainable Development Goals aim that by 2030, all countries should have an under-5 mortality rate of ≤25 deaths per 1,000 live births, and a neonatal mortality rate of ≤12 deaths per 1,000 live births.[1] Unfortunately, many countries will still not be able to meet these goals, and maternal mortality also remains a problem. Prior to the COVID-19 pandemic, child mortality was the lowest it had ever been dropping from 12.6 million in 1990 to 5 million in 2020.[2] Child, neonatal, and maternal deaths are mostly concentrated in Africa, South America, and Asian countries. Of the 5 million deaths which occurred in 2020 in under-5s, almost half were in newborns (0–27 days of age). The leading causes of diseases in under-5s are still infectious diseases, preterm birth complications, birth asphyxia and trauma, and congenital abnormalities.[3]

Maternal immunization can provide a continuum of protection across the period from birth to 3 months of age, where infants are too young to be vaccinated or receive full benefit from vaccination. Currently, vaccines against 4 pathogens are generally recommended during pregnancy (tetanus, pertussis, influenza, and SARS-CoV-2), while a number of others (e.g., meningococcal) are recommended in certain situations. RSV and GBS vaccines are in late-stage clinical trials, and there are a number of vaccines for potential maternal use which are in earlier stages of development or could be considered for research, including malaria, Ebola, hepatitis E, and CMV.

Dr Muñoz discussed the lessons learned from the COVID-19 pandemic, where despite pregnant women being identified early on as being at increased risk for severe disease and adverse pregnancy outcomes, they remained excluded from all initial vaccine trials. However, pregnant women were eventually included in recommendations for vaccination, and were prioritized based on CDC and ACOG guidance. Inclusion of pregnant women in COVID-19 vaccination strategies was based on risk-benefit analysis and pre-clinical/clinical data on the mRNA vaccine platform. Eventually, other vaccine platforms have also been recommended



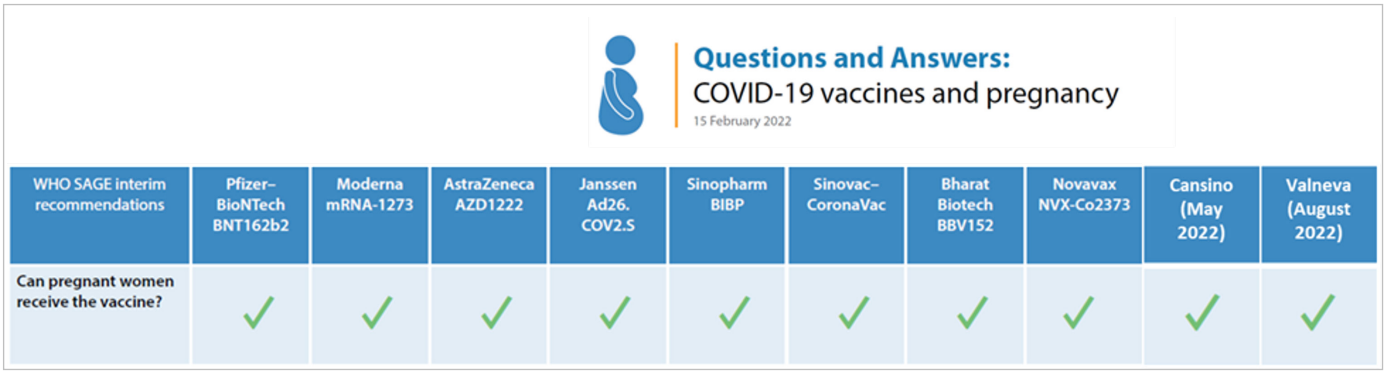
for use in pregnant women, although data from these platforms remains limited.[4]

Data from surveillance systems and observations studies have shown that COVID-19 vaccines are as immunogenic in pregnant as in non-pregnant women, are not associated with any increased risk of miscarriage, stillbirth, or fetal/neonatal complications, and can help protect against severe disease in infants.[5] The potential risk of rare side effects (e.g. thrombosis with thrombocytopenia syndrome) highlight the need for specialized surveillance to monitor the impact of vaccines across populations.

Dr Muñoz concluded by discussing upcoming vaccines for use during pregnancy, including vaccines against RSV and GBS. RSV is the most important cause of LRTI in infants and young children. Approximately 2–3% of infections result in hospitalization and >75% of disease occurs in healthy, full-term infants. Mortality is higher than for influenza or COVID-19, and severe infection may be associated with subsequent chronic diseases e.g., asthma. While RSV occurs globally, >99% of deaths occur in LMICs and nearly half in infants <6 months of age,[6,7] meaning that prevention needs to occur very early in life or during pregnancy. Despite the use of palivizumab for high-risk babies, data from the US New Vaccine Surveillance Network has shown that there is still a substantial disease burden, with highest hospitalization rates in infants <1 month of age, and 67% of those infected with RSV having no underlying comorbid conditions or preterm birth.[8] Therefore, there remains an unmet need for prevention of RSV in very young infants.

Following on from the first attempts to develop an RSV vaccine in the last 1990s, a number of RSV vaccines and monoclonal antibodies are under development (see https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/). These include an RSV F nanoparticle vaccine developed by Novavax which completed a phase 3 study but failed to meet the study's primary efficacy endpoint. Despite this, the vaccine did result in a significant risk reduction in all-cause pneumonia (further details of the trial are presented on Day 2 of this meeting). A phase 3 trial of the GSK pre-fusion F subunit vaccine was stopped in 2022 possibly due to safety concerns, and a phase 3 trial of another pre-

fusion F subunit vaccine by Pfizer is ongoing (detailed results are presented on Day 2 of this meeting). Topline data for this vaccine showed efficacy of 81.8% against RSV-positive severe medically-attended LRTI through 90 days of life, and 69.4% in the first 6 months, with no identified safety concerns. Monoclonal antibody data from phase 2 and 3 trials is also promising, with vaccine efficacies of approximately 70–75% up to 150 days in preterm and full-term infants.[9] There are a number of considerations for both maternal vaccination and infant passive antibodies for prevention of RSV:



Questions and Answers:
COVID-19 vaccines and pregnancy
15 February 2022

WHO SAGE interim recommendations	Pfizer–BioNTech BNT162b2	Moderna mRNA-1273	AstraZeneca AZD1222	Janssen Ad26.COV2.S	Sinopharm BIBP	Sinovac–CoronaVac	Bharat Biotech BBV152	Novavax NVX-Co2373	Cansino (May 2022)	Valneva (August 2022)
Can pregnant women receive the vaccine?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Phase 2 and 3 trials of multivalent conjugate vaccines are also underway for prevention of GBS disease, which is the most common cause of neonatal sepsis. GBS occurs worldwide but colonization rates are highest in Africa and Asian regions.[10] Further details of the latest data on GBS vaccines are presented in later talks in this meeting, together with an update on current research on vaccines against Lassa fever and hepatitis E for use in pregnancy.

Dr Muñoz concluded her talk with a brief discussion of the role of translation and implementation science to promote the uptake, adaptation and maintenance of evidence-based practices in design, development, and implementation of vaccination during pregnancy. This includes ways to reduce vaccine hesitancy and to include pregnant women earlier in the research and development process at a global level. In addition, there were a number of other lessons learned from the COVID-19 pandemic that will help support efforts of maternal immunization including: the need to have safety surveillance systems already in place, prior to the next outbreak or pandemic, to monitor vaccine safety; to proactively plan for which data will be needed to be collected for key decision making regarding vaccination during pregnancy; to have knowledge of background maternal and infant outcomes; and to be proactive in establishing collaborations and sharing results of research so that these can be utilized early in the next potential outbreak.

SESSION 1: THE IMPACT OF COVID-19 ON PREGNANCY

COVID-19: BURDEN OF DISEASE AND VACCINE POLICY — A GLOBAL PERSPECTIVE

Dr Mercedes Bonet, Medical Officer in the Maternal and Perinatal Health Team, Department of Sexual and Reproductive Health and Research at the WHO, began the session by giving an overview of the global burden of COVID-19 disease and variations in vaccine recommendations for pregnant women.

In April 2020, a living systematic review was initiated to evaluate clinical presentation, mother-to-child transmission, outcomes, and risk factors in pregnant women. The review identified that pregnant women are more likely to require ICU admission and invasive ventilation than non-pregnant women, and those with COVID-19 are more likely to have adverse outcomes including preterm birth, stillbirth, neonatal deaths, and caesarean section than pregnant women without COVID-19.[11] In addition to overall increased risk, comorbidities including increased maternal age, high body mass index, gestational diabetes, and hypertensive disease were associated with severe COVID-19 during pregnancy.[11,12] The review has also shown that mother-to-child transmission is low, with <3% of babies having SARS-CoV-2 positivity at any point in time. Positivity rates were higher in infants born to women with more severe disease, but were not associated with infant disease severity, gestation, separation at birth, or breastfeeding. Additionally, positivity was higher in babies born by caesarean section, although the reasons behind this are not completely clear.[13]

Although pregnant and lactating women were not included in initial clinical trials of COVID-19 vaccines, it was unlikely that the vaccines would pose additional risks during pregnancy as they were not live virus vaccines. In addition, data from animal studies and early surveillance did not indicate any harmful effects during pregnancy. Reasonably early in the roll-out, pregnant women were identified as a priority for vaccination, and there are now 10 vaccines recommended by the WHO which can be used in this population.[14]

COVID-19 vaccination before or during pregnancy is especially important in settings of moderate-to-high community transmission and for those at increased risk of exposure or severe disease.[15] The WHO does not recommend delaying or terminating pregnancy because of COVID-19. No pregnancy testing is required prior to vaccination and breastfeeding is not contraindicated because of vaccination. WHO also recommends that a booster dose is offered 4–6 months after the primary series, with a second booster for high-risk groups, including pregnant women.[16] Despite these recommendations, national policies vary, with 11 countries globally still not recommending vaccination for any pregnant women as of October 2022 (https://www.comitglobal.org/explore/public-health-authorities/pregnancy).

The WHO have published a manual on safety surveillance for COVID-19 vaccines, with a specific module on vaccination in pregnancy.[17] Both active and passive surveillance approaches are recommended, including in pregnant women.

ACOG: VACCINE RECOMMENDATIONS AND THE ROLE OF PROFESSIONAL SOCIETIES

Dr Richard Beigi, President of UPMC Magee-Women's Hospital and an active member of ACOG Immunization Expert Group summarized ACOG's role in developing guidance for pregnant women about COVID-19 disease and the risks and benefits of vaccination.

Dr Beigi began by providing an overview of the timelines that led to ACOG's initial COVID-19 response, with the first practice advisory released in Feb 2020. In March 2020, ACOG developed a set of frequently asked questions (FAQs) which addressed many of the queries received in the first few months of the pandemic, including use of personal protective equipment, managing patients in person and remotely, and optimizing use of personnel and resources. As questions were being

asked from a wide array of areas, ACOG formed working groups of key leaders and experts to focus on providing guidance on specific topics such as obstetrics, ethics, and telehealth. By the summer of 2020 it appeared that pregnant women were likely to be left out of impending vaccine roll-out efforts, due to not being included in vaccine investigations and thus lacking relevant data. ACOG was actively involved in trying to encourage companies and regulators to include pregnant women in vaccine development. As there was no biologic plausibility for an increased risks from vaccination in pregnant women versus non-pregnant adults with available vaccines (mRNA-based), and it was becoming increasingly clear that they were at an increased risk of severe disease, ACOG advocated and recommended that pregnant women should be able to access COVID-19 vaccines as soon as available based on their own autonomous decision making (in collaboration with their providers as needed). After roll-out began, data from the CDC's V-safe program increasingly demonstrated that there were no increased rates of adverse events or reactogenicity of mRNA vaccines during pregnancy. Based on these data, and other evolving data sources, ACOG made a more definitive recommendation for vaccination with mRNA vaccines to pregnant women in July 2021, 7 months after the first vaccine availability. This recommendation has now been extended to cover other vaccine platforms (e.g., protein-based vaccines such as Novavax) and updated to include the importance of monovalent and bivalent boosters.

Guidance is continuing to evolve based on endemicity and increasing informative data, and ACOG remains committed to addressing misinformation in order to increase vaccine confidence. Potential concerns which are being addressed are the risk of co-circulating influenza and COVID-19 after lifting of social restrictions, and the potential for new threats during pregnancy, such as mpox.

Data from a 2021 member survey given to ACOG's constituency showed that the ACOG guidance was a useful resource both for patients and professionals during the COVID-19 pandemic. The majority of members who responded were satisfied or extremely satisfied with the available clinical, health equity, and practice management resources provided by ACOG and their education and advocacy efforts. Opportunities for further improvements include creating videos to help physicians explain mRNA technology to patients, increased consistency of guidance (although this was evolving over time), and more efforts in addressing misinformation.

DEVELOPING POLICY FOR MATERNAL COVID-19 IMMUNIZATION: LESSONS LEARNED FROM THE PANDEMIC

Dr Dana Meaney-Delman, Chief of Infant Outcomes Monitoring, Research, and Prevention, and Dr Kara Polen, Associate Director of Communications in the Division of Birth Defects and Infant Disorders at the CDC provided an overview of maternal COVID-19 vaccination policy in the US, and the lessons learned from the pandemic experience.

In October 2020, discussions around COVID-19 vaccines were mainly focused on the theoretical risks of vaccination with the new mRNA vaccines, rather than the potential benefits. The FDA indicated that DART studies of COVID-19 vaccines would need to be performed before potential enrollment of pregnant women in clinical trials, and that follow-up in pregnant populations (including pregnancy exposure registries) was needed to monitor outcomes. By December 2020, the first COVID-19 vaccine was authorized for use, and the V-safe system was launched. At this time there was only limited data available in pregnancy because pregnant persons were excluded from all pre-authorization clinical trials; however, obstetrics and vaccine experts agreed that the theoretical risks of non-live COVID-19 mRNA vaccines were unlikely given what was known about vaccines during pregnancy. Experts also agreed there were known potential benefits to the pregnant person, and to the pregnancy. Given the limited data available and recognizing the known benefits, CDC recommended that pregnant women should be offered the same opportunity to receive COVID-19 vaccines as non-pregnant women if they were in an eligible group determined by ACIP, without the need for physician approval. Therefore, pregnant women were considered and included in each phase of vaccine roll-out, based on the risk group determined by ACIP. Despite these recommendations, states varied in their approach to prioritizing pregnancy as a qualifying condition, with only 15 states including

pregnant women in phase 1 priority as of February 2021 (https://marlin-prod.literatumonline.com/pb-assets/Health%20Advance/journals/ymob/YMOB_13697.pdf). The main challenge was theoretical concerns over safety in general (not just for pregnant people but there were additional major concerns about the risks to the developing fetus, the pregnancy, and future fertility) and countering extensive misinformation. While the Vaccine Adverse Event Reporting System (VAERS), Vaccine Safety Datalink (VSD), and Clinical Immunization Safety Assessment (CISA) project vaccine monitoring systems were already in place, the V-safe smartphone-based monitoring system was set up specifically for monitoring COVID-19 vaccines in a real-time fashion to provide safety information as quickly as possible. Within the V-safe system, questions were asked about pregnancy, and pregnant persons were given the option to enroll in the pregnancy registry, if eligible. Enrolling in the registry included a 20-min telephone interview, several call backs during the pregnancy and around the time of the due date, and providing consent to access to medical records, if desired. One important feature was working with the phone companies to set up a caller ID system where participants were called by a number identified as the CDC, which, according to enrollees, aided in increasing the number of people answering calls. Surprisingly, the V-safe pregnancy registry enrollment increased rapidly, with 1815 women enrolled within a month of launch. Early safety data analyses showed reactogenicity during pregnancy was similar to non-pregnant women, with no concerning safety signals.[18] This was supported by data from later in summer 2021, which demonstrated no increased risk of spontaneous abortion, and early findings on effectiveness and transfer of maternal antibodies to the neonate.[19-22] At this point, the Delta variant began to predominate, with high numbers of cases and increased rates of severe outcomes, including deaths, in pregnant women. In August 2021, the CDC updated guidance to strongly recommend vaccination before and during pregnancy. However, coverage rates during pregnancy remained low, with an overall coverage of 32.5% as of November 2021, with the lowest uptake in black non-Hispanic individuals. Current estimates (November 2022) are that 72–77% of currently pregnant women have received a primary series (mostly prior to becoming pregnant), and 48–60% have received a booster. As of August 2022, 22,953 pregnant women had been included in the V-safe pregnancy registry, representing 98% of individuals who were eligible and contactable. 45% of whom were healthcare workers.

CDC continues to work towards improving vaccine coverage by ensuring consistent recommendations among healthcare workers giving advice to pregnant women, recruiting vaccine champions of diverse backgrounds to promote the benefits of vaccination, increasing vaccine providers, and sharing testimonials from pregnant women and their families to help increase confidence among reproductive age and pregnant people.

Overall, a number of lessons were learned from the COVID-19 pandemic which should be taken into account for future outbreaks/pandemics:

Maternal Vaccine Policy: Lessons Learned from the Pandemic

- In the absence of safety data, the theoretical risks of the vaccine to pregnant women and the fetus are weighed more heavily
- OB/GYN vaccine expertise and engagement with clinical organizations is essential to balance the risk-benefit discussion
- Misinformation is a powerful deterrent to implementation of vaccine recommendations for pregnant people and without safety data it takes hold
- Rapid capture of safety data is possible and can have a major influence on vaccine policy and uptake
- Healthcare workers, as early adopters, are willing to share their experiences to inform vaccine policy and reliably report outcomes
- Demonstrating fetal and infant benefit is critically important

PANEL DISCUSSION 1: VACCINE POLICY FOR COVID-19 AND EMERGING INFECTIOUS DISEASES WITH IMPACT ON PREGNANCY

Prof Shabir Madhi, Dean and Professor of Vaccinology at the University of the Witwatersrand, South Africa, moderated the first panel discussion. Panel members were Dr Mercedes Bonet Semenas, Dr Dana Meaney-Delman, Dr Richard Beigi, and Prof Geeta Swamy, Professor of Obstetrics and Gynecology at Duke University.

The following topics were discussed during the session:

1. **In hindsight, was it correct to exclude pregnant women from vaccine development, given that the efficacy of the vaccines was not known and they were based on novel technologies?**

   The panel considered that exclusion of pregnant women from vaccine development was a missed opportunity and led to delays in access to vaccines for this population. It became evident early in the pandemic that pregnancy was a risk factor for severe disease, and there was a lack of alternative treatment options for this population. Waiting to see if vaccines were efficacious before performing any specific studies in pregnant women was a missed opportunity, as small-scale safety studies could have been performed in parallel when it was evident that there were no serious safety concerns. Setting up specific studies upfront would also have been important as many frontline healthcare workers are women of reproductive age, and therefore could potentially have become pregnant before or after receiving the vaccine. The view of risk should be changed from focusing on the theoretical risk of a vaccine to evidence-based risk:benefit evaluations, focusing on the risk of the disease versus the risk of the vaccine. While it is important to acknowledge any potential biological risk, this was not expected from mRNA vaccines due to their mode of action.

2. **Why was SAGE proactive from early in the pandemic about access to the vaccines for pregnant women?**

   SAGE was relatively proactive early in the pandemic because it became evident that pregnant women were at an increased risk of complications from COVID-19, as had been the case with previous respiratory virus outbreaks. Early guidance stating that pregnant women should be able to access vaccines was based on risk:benefit assessments, with V-safe data being key in switching this advice to a recommendation.

3. **Should pregnant women receive a booster dose of COVID-19 vaccines, given the uncertainty of when the next wave will arrive and the drop in effectiveness 20 weeks post-vaccination?**

   Booster vaccination is advised, as it is better to reduce the risk of disease every 4–6 months than have a largely unprotected population when the next wave arrives. However, given the challenge imposed by emerging SARS-CoV2 variants and the need for repeated vaccinations, vaccine fatigue is a major issue, and many people are reluctant to have any further vaccinations. In general, vaccination for pregnant women against COVID-19 should follow the guidance for the general population. For LMICs in particular, there is the issue of prioritizing which vaccines to give, as large percentages of the population may have immunity from natural infection (up to 90% in South Africa) and other diseases may be a greater risk and priority. The number of vaccines offered during pregnancy could also be a consideration, as many women will be reluctant to have multiple vaccines once they become available. Co-administration and possible combination vaccines should be evaluated.

SESSION 2: EVALUATING SAFETY AND EFFECTIVENESS OF VACCINES FOR PREGNANT WOMEN

COVID-19 VACCINES AND PREGNANCY: LIVING SYSTEMATIC REVIEW

Dr Pierre Buekens, Director of the Center for Emerging Reproductive and Perinatal Epidemiology at Tulane University started the second session of the day by demonstrating the Safe in Pregnancy living systematic review dashboard.

Safe in Pregnancy (safeinpregnancy.org) was developed as a resource for collating all the information available on COVID-19 vaccines in pregnancy but can also be used in the future as a resource for other vaccines administered to pregnant women. The current focus of research is the Living Systematic Review, which is regularly updated with data from studies including pregnant women as the publications/pre-prints become available. Most of the studies are comparative, and as of 8th November 2022, 121 studies had been collected covering a population of approximately 885,000 pregnant women globally. The vast majority of studies are on mRNA vaccines, but data are also becoming available on other platforms including viral vector and inactivated virus vaccines. Professor Buekens demonstrated the capabilities of the application available online. The dashboard allows filtering by e.g., publication data, country, outcome, vaccine with direct links to all the publications included in the review.

The dashboard also links to a meta-analysis which is fed automatically from the database. Within the meta-analysis, outcomes can be selected, and any eligible papers are included. However, only studies which adjust for confounders are included in the meta-analysis, therefore there are many less than are included in the systematic review as a whole.

OVERCOMING COVID-19: COVID-19 MATERNAL VACCINE EFFECTIVENESS AGAINST INFANT HOSPITALIZATION

Dr Natasha Halasa from Vanderbilt University Medical Center and Ms Samantha Olson from the CDC provided an overview of a study performed by the Overcoming COVID-19 Network, evaluating the effectiveness of maternal COVID-19 vaccination during pregnancy against hospitalization in infants <6 months of age.

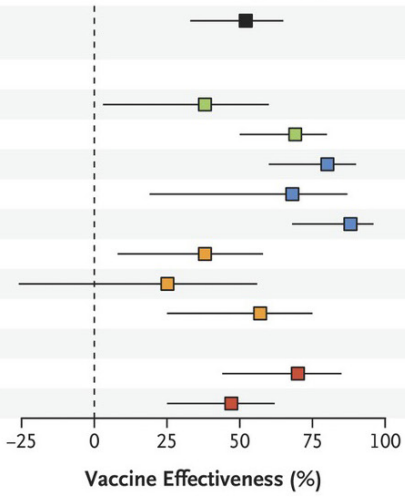
COVID-19 during pregnancy is associated with severe illness, hospitalization and death, and can increase the risk of adverse pregnancy outcomes and neonatal complications. mRNA vaccines received during pregnancy have been highly effective and are recommended by the CDC for all persons 6 months and older, including pregnant and lactating people, and those wishing to become pregnant in the future. Maternal antibodies following infection or vaccination have been found in cord blood, breast milk, and infant serum,[23-25] with antibody titers following maternal vaccination that are highest in infants when the mother was vaccinated late in the second trimester or early in the third trimester. Antibodies can persist for the first 6 months of life, with higher titers in infants whose mothers were vaccinated than those born to mothers with natural infection.[26] Infants <6 months of age are at high-risk for complications of COVID-19 but are not eligible for vaccination. During the peak period of B.1.1.259 circulation (omicron), hospitalization rates for infants <6 months were 6 times higher than during the delta variant peak, and this age group accounted for 44% of COVID-19-related hospitalizations in children ≤4 years of age.[27] Therefore, maternal vaccination can be an important tool in preventing severe disease in young infants.

The Overcoming COVID-19 Network led by Dr. Adrienne Randolph at Boston Children's Hospital was created to understand the impact of severe COVID-19 on children and infants. Overcoming COVID-19 is a network of over 70 hospitals across the US and was developed from a network set up during the 2009 Influenza A/H1N1 pandemic to monitor critical influenza illness in pediatric patients.[28,29] In 2022, a pilot study across 20 of the Overcoming hospitals determined maternal vaccine effectiveness during pregnancy against COVID-19 hospitalization in infants <6 months of age was 61% (95% CI: 31–78%), based on data from 379 infants hospitalized primarily during the delta-period.[30] Based on this pilot, a larger-scale study was performed across the delta and omicron periods (July 2021 to March 2022) evaluating the impact of maternal vaccination on infant hospitalization based on timing of vaccination receipt during pregnancy and disease severity.[5] Case infants had a positive RT-PCR or antigen test within 10 days of symptom onset or within 72 hours of hospital admission and were admitted with COVID-19 as the primary reason for admission or had clinical symptoms associated with COVID-19. Control infants tested negative for COVID-19, with or without COVID-19-associated symptoms. The study was a test-negative design, and maternal full vaccination was defined as completion of two doses of mRNA-1273 or BNT162b2 during pregnancy at least 14 days prior to delivery. To estimate vaccine effectiveness, we used logistic regression, where the odds of maternal vaccination were compared among case infants and control infants. Estimates were adjusted for infant age, sex, race/ethnicity, US census region, and calendar time. Overall, 537 case infants and 512 control infants were included, of whom 16% and 29% were born to fully vaccinated mothers, respectively. Median age of case and control infants was 2 months, and a lower percentage of case infants were non-Hispanic white, had higher social vulnerability index scores, and were less likely to have an underlying condition in comparison to control infants. Pre-term birth was more common in infants born to unvaccinated mothers than those vaccinated.

Overall, 2 doses of mRNA maternal vaccination during pregnancy prevented over half of infant hospitalizations with COVID-19. Vaccination later in pregnancy (>20 weeks gestation) had a higher effectiveness against hospitalization than during the first 20 weeks of pregnancy (69% vs 38%), with the highest effectiveness during the delta-predominant period [68% (95% CI: 19 to 87%) with the first 20 weeks vs 88% (95% CI: 68 to 96%) >20 weeks]. Vaccine effectiveness was lower during the omicron period, but still demonstrated higher effectiveness >20 weeks compared to early in pregnancy [57% (95% CI: 25 to 75%) vs 25% (95% CI: -26 to 56%)]. Maternal vaccination also prevented severe illness in infants and was 70% effective against infant ICU admission. Overall, 90% (102/113) of case infants admitted

to the ICU with COVID-19 were born to unvaccinated mothers. Further, two case infants in the cohort died from COVID-19, and 2 case infants received ECMO (extracorporeal membrane oxygenation); none of the 4 infants' mothers had been vaccinated during pregnancy.

Subgroup	Case Infants	Control Infants	Effectiveness of Maternal Vaccination
	no. of vaccinated mothers/total no. (%)		*% (95% CI)*
Overall effectiveness of maternal vaccination	87/537 (16)	147/512 (29)	52 (33 to 65)
Timing of vaccination			
During first 20 wk of pregnancy	46/496 (9)	62/427 (15)	38 (3 to 60)
After 20 wk of pregnancy	31/481 (6)	79/444 (18)	69 (50 to 80)
Delta-predominant period	14/181 (8)	61/216 (28)	80 (60 to 90)
Vaccinated during first 20 wk of pregnancy	8/175 (5)	22/177 (12)	68 (19 to 87)
Vaccinated after 20 wk of pregnancy	5/172 (3)	37/192 (19)	88 (68 to 96)
Omicron-predominant period	73/356 (21)	86/296 (29)	38 (8 to 58)
Vaccinated during first 20 wk of pregnancy	38/321 (12)	40/250 (16)	25 (−26 to 56)
Vaccinated after 20 wk of pregnancy	26/309 (8)	42/252 (17)	57 (25 to 75)
Type of hospital admission			
ICU	11/113 (10)	147/512 (29)	70 (42 to 85)
Non-ICU	76/424 (18)	147/512 (29)	47 (25 to 62)



Overcoming COVID-19 is continuing to collect data on infants with severe COVID-19, with the aim of filling knowledge gaps including the effect of boosters received during pregnancy, timing of maternal vaccination, against new emerging COVID-19 variants, and to calculate vaccine effectiveness by infant age.

EVALUATING THE SAFETY AND IMMUNOGENICITY OF HEPATITIS E VACCINE IN PREGNANT WOMEN

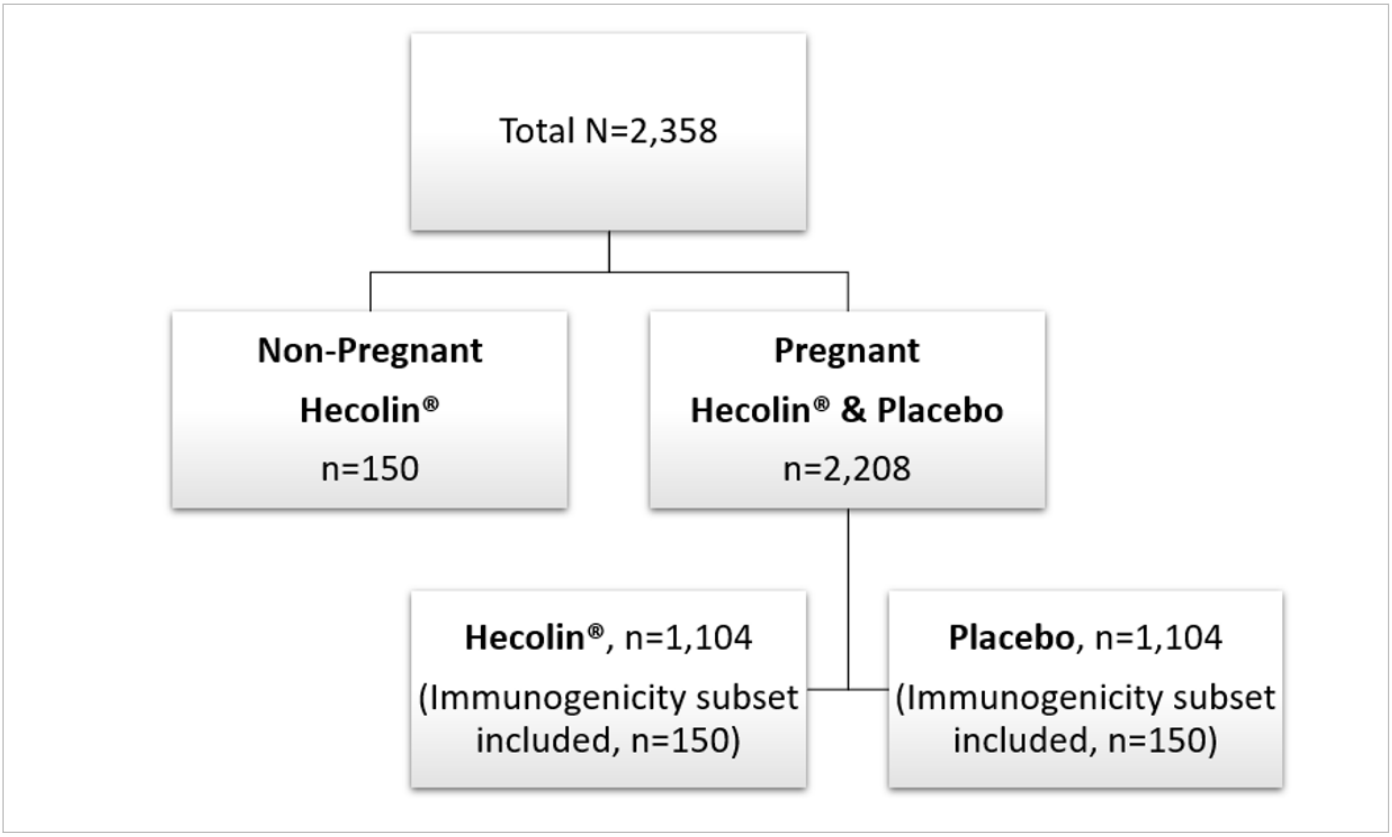
Dr Katerina Rok Song, Research Scientist at the International Vaccine Institute in Seoul, South Korea, provided an overview of the ongoing clinical trial evaluating the safety and immunogenicity of a hepatitis E (HEV) vaccine in pregnant women.

HEV was first identified in 1981 and has four genotypes that infect humans. Most cases are mild or asymptomatic, and the case fatality rate is 1–2% in the general population but is 20–40% in pregnant women. The disease burden is highest in Africa and Southeast Asia, with a particularly high burden in pregnant women. Overall, HEV accounts for approximately 10% of all deaths during pregnancy. Mortality from HEV is highest in the third trimester and has been associated with high rates of intrauterine death and pre-term delivery.[31,32]

Hecolin®, an alum adjuvanted recombinant viral-like particle HEV vaccine, is licensed as a three-dose schedule in China and Pakistan. In the pivotal phase 3 clinical trial of approximately 120,000 subjects aged 16–45 years (excluding pregnant women), the vaccine demonstrated 100% efficacy against hepatitis E at 1 year and 93% at 4.5 years.[33,34] Although excluded, 37 pregnant women were inadvertently vaccinated during the trial. Safety data in these women showed that the vaccine was well tolerated, although unfortunately no immunogenicity data were available. Although licensed for the general population in China and Pakistan, the WHO does not recommend routine use of the vaccine in pregnant women due to a lack of sufficient information on safety, immunogenicity, and efficacy. However, they do state that the vaccine should be considered in high-risk groups, such as pregnant women.[35]

Dr Song then described the design of an upcoming phase 2 study of the vaccine during pregnancy, which will be evaluated in healthy pregnant and non-pregnant

women. The first participant enrolment is expected in March 2023, with an estimated trial duration of 24 months. For pregnant participants, two doses of the vaccine will be administered 4 weeks apart during pregnancy. A third dose will be administered after delivery. Primary objectives are rates of pregnancy-related adverse events of special interest (AESIs) and serious AEs compared with placebo, and non-inferior immunogenicity in pregnant women vs non-pregnant women at 4 weeks post-second dose, based on geometric mean concentrations of anti-HEV IgG. Safety follow-up will be performed for mothers and infants throughout the study (up to 6 months post-birth), and antibody levels will be evaluated in cord blood, maternal and infant serum, and breastmilk. In total, 2358 individuals will be enrolled.



The sample size was calculated by a precision-based approach using an equivalence margin for safety event rates of 5% of more. The study is being performed across 4 satellite sites in Karachi, Pakistan, in collaboration with Aga Khan University. Inclusion criteria for pregnant women include age 16–45 years who are between 14 0/7 and 34 6/7 weeks gestation on the day of planned vaccination with an uncomplicated, singleton pregnancy, and who are at no known increased risk for complications. Non-pregnant women aged 16–45 years were also eligible for enrolment in the non-pregnant arm of the study. Key exclusion criteria include previous HEV vaccination, but individuals with previous HEV infection are permitted.

Last subject last visit is expected in Q1 2025 with study results available during Q2 of 2025. The results of the trial will hopefully facilitate decision-making and recommendations for the use of the vaccine during pregnancy and lead to an updated package label regarding safety and immunogenicity in pregnancy. This study represents a scenario where an available safe and effective vaccine with the potential for benefit in pregnant women could be evaluated for specific indication in pregnancy.

PANEL DISCUSSION 2

Prof Flor Muñoz moderated the second panel discussion. Panelists were Dr Pierre Buekens, Dr Natasha Halasa, Dr Samantha Olson, Dr Katerina Rok Son, Dr Leila Sahni from Baylor College of Medicine, Dr Andy Stergachis from the University of Washington, and Dr Nicky Klein from Kaiser Permanente Vaccine Study Center. The following topics were discussed:

1. **Additional data from a Kaiser Permanente study of COVID-19 vaccination in pregnant women**

   Results of the study have recently been presented at ID Week.[36] Vaccine effectiveness in the cohort of pregnant women evaluated was similar to that seen in non-pregnant women, with estimates of approximately 80% across vaccines in the initial COVID-19 period, approximately 70% in the delta predominant period, and approximately 25% in the omicron predominant period (which increased to 58% after a booster dose). Overall, 109 pregnant women were hospitalized, of whom 10 had been fully vaccinated with a primary series. None of these women had severe disease or required ICU admission, compared with 10–20% of unvaccinated women.

2. **Safety surveillance**

   Safety data for vaccines in LMICs are lacking, especially for non-mRNA vaccines that are available for use in pregnant women in these countries (as most safety data in pregnancy is from countries that utilize mRNA vaccines). Safety surveillance should ideally leverage existing systems including pregnancy registries and data collected by the maternal health and epi communities. An example of this was the use of the HIV trials network during the pandemic. While pharmacovigilance data have been collected in LMICs, in conjunction with the WHO, this has focused on the general population and not pregnant women, therefore further data are needed on pregnancy outcomes.

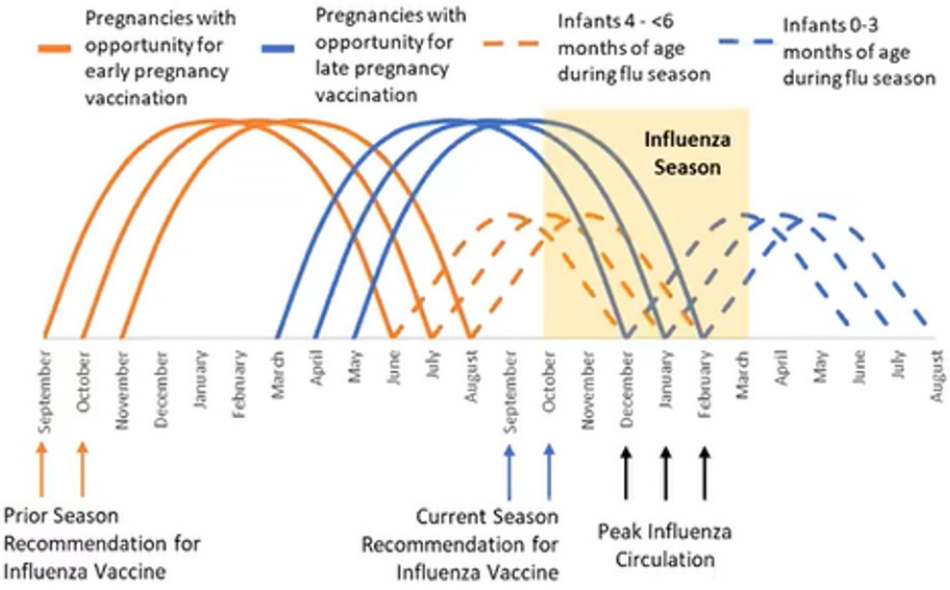
3. **What were the challenges associated with implementing the HEV vaccine study?**

   One major challenge was the need to perform the study in a high-risk area and LMIC. HEV is generally associated with extreme poverty, and data on pregnancy outcomes is very lacking in these populations, and no surveillance systems are in place. The site in Pakistan was chosen as it had been used for a previous pregnancy outcomes study funded by the Bill and Melinda Gates Foundation, therefore data on background rates of pregnancy outcomes are available and were used as a base for sample size calculations for the trial. However, there are many factors which influence outcomes, therefore it would be preferable to match participants with other pregnant women (e.g., test negative design).

4. **How can the lessons learned from estimating vaccine effectiveness for COVID-19 vaccines be used for other vaccines (e.g., RSV)?**

   The seasonality of RSV creates an additional challenge for evaluating vaccine effectiveness and decisions on when and who to vaccinate, as risk of infant infection and trimester of vaccination vary depending on the time of year, as with influenza:

Figure. Seasonal Influenza enrollment scenarios for infants <6 months of age in the context of maternal vaccination during pregnancy



Ideally, we need more data on antibody titers and waning, which could be used in conjunction with virus surveillance for decision making about when the best time is for vaccination.

5. **What are specific concerns for LMICs going forward?**

   Experience from systems set up for monitoring outbreaks of Ebola have demonstrated that they are not used in between outbreaks and have to be reinstated each time. Ideally any newly developed surveillance systems should be linked to a disease that is constantly/seasonally circulating (e.g., influenza) to ensure that continues to be used in between outbreaks. An additional concern for new maternal vaccines is that the predictability of vaccine effectiveness in LMICs differs to that in HICs, as transplacental antibody transfer rates are lower in LMICs. In addition, basing a vaccine's potential on outcomes assessed in clinical trials can lead to under-appreciation of the public health benefits (e.g., against all-cause pneumonia).

6. **Has vaccine fatigue spilled over from COVID-19 to other vaccines?**

   This is currently being evaluated in the US. As of April 2022, influenza vaccination rates during pregnancy appear to be lower than previous years (https://www.cdc.gov/flu/fluvaxview/pregnant-women-apr2022.htm).

The panel discussion closed Day 1 of the meeting.

MEETING SUMMARY: DAY 2

Time (PDT)	Session	Speaker
8:00 am	**Session 1**	*Moderator*: Flor Muñoz
8:00 am	Maternal GBS vaccine development	Bill Gruber
8:20 am	Early onset GBS during the pandemic in Spain	Concepción de Alba Romero
8:30 am	Current challenges of monkeypox vaccine	Asma Khalil
8:50 am	IMPRINT for maternal immunization	Chrissie Jones
9:10 am	CEPI portfolio- considerations for pregnant women	Gerald Voss
9:20 am	Q&A	
9:30 am	**Session 2**	
9:30 am	RSV maternal vaccine program – background and latest updates	Bill Gruber
9:50 am	Lessons learned from PREPARE Maternal RSV vaccine trial	Shabir Madhi
10:10 am	Update on monoclonal antibodies for RSV prevention in infants	Octavio Ramilo
10:30 am	Q&A	
10:40 am	Break	
11:00 am	**Panel Discussion 1**	
	Panelists: 1. Bill Gruber 2. Chrissie Jones 3. Asma Khalil 4. Octavio Ramilo 5. Katerina Song 6. Karin Bok 7. Kirsty Le Doare 8. Shabir Madhi	*Moderator:* Janet White
11:10 am	Break	
11:45 am	**Panel Discussion 2**	
	Panelists: 1. Bill Gruber 2. Gerald Voss 3. Danny Feikin 4. Niranjan Bhat 5. Jessica Fleming 6. Azucena Bradaji 7. Esperanca Sevene 8. Kirsty Le Doare	*Moderator:* Ros Hollingsworth
12:30 pm	Open Q&A/Discussion, meeting conclusions, next steps	*Moderator*: Flor Muñoz

SESSION 1: EVALUATING THE SAFETY AND EFFECTIVENESS OF FUTURE VACCINES FOR PREGNANT WOMEN

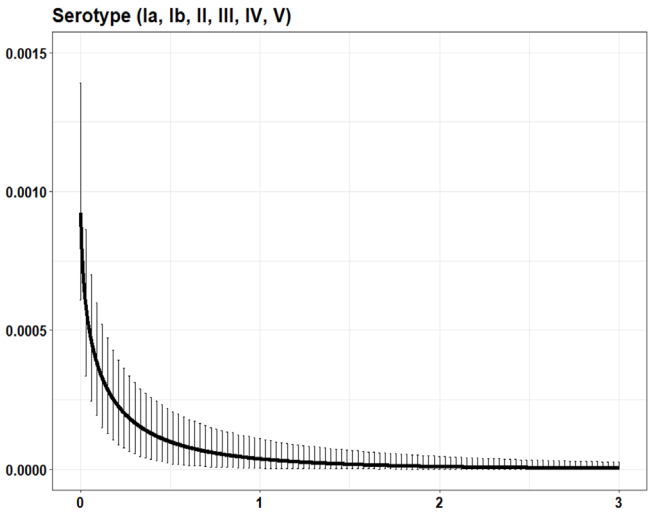
The focus of Day 2 of this workshop was the future of maternal immunization, including discussions on upcoming vaccines and how the MIWG can help these vaccines be accessible to pregnant women.

MATERNAL GBS VACCINE DEVELOPMENT

Dr William Gruber, Senior Vice President of Vaccine Clinical Research and Development at Pfizer started the session with an update on maternal GBS vaccine development. GBS is the most frequent cause of serious bacterial infections in newborns. Of the 6 serotypes of GBS, serotypes Ia and III are the most common, and overall it is estimated that GBS colonizes the vaginal and rectal tracts of approximately 25% of pregnant women globally. GBS causes a significant burden across LMICs and HICs,[10] and there are currently no licensed vaccines to prevent GBS disease. Universal screening and antibacterial prophylaxis during labor has reduced the incidence of early onset disease (EOD; 0–6 days of age) in the US but has not had an impact on late onset disease (LOD; 7–89 days of age).[37]

In the 1970s, Carol Baker's lab demonstrated that maternal antibodies against the GBS capsular polysaccharide (CPS) could potentially provide protection against infant GBS disease. In the study, none of the infants who developed GBS disease had mothers with CPS antibodies, compared with 76% of mothers of infants who did not develop GBS disease.[38] In addition to this early study, proof of principle research in a mouse model has demonstrated that active immunization with a six valent vaccine results in passive transfer of anti-CPS maternal antibodies which were protective against disease from any of the six serotypes.[39]

One of the challenges of GBS vaccine development has been the path to licensure, due to the large numbers of subjects who would need to be enrolled in an adequately powered phase 3 efficacy study. Therefore, a seroepidemiological approach has been preferred, which would use data from studies to estimate an antibody threshold which could then be used as a surrogate of protection. Such an evaluation would be followed by post-approval efficacy or effectiveness studies in at-risk populations. While a number of seroepidemiological studies have been performed, differences between study designs and assays means they are not easily comparable. Pfizer therefore has developed a standardized assay to use in their vaccine trials. This has been used in a prospective cohort study in South Africa, which included 17,752 mother-infant dyads enrolled between March 2019 and June 2020. Matched controls were infants with GBS born to colonized mothers, and the study focused on serotypes Ia and III. The study found that anti-CPS IgG titers were significantly higher in controls vs cases for both serotypes. Using a Bayesian approach, risk curves were generated across serotypes which can be used to show the probability of protection by antibody concentration, and therefore the predicted level of protection from a vaccine (Figure).



The Pfizer six valent vaccine is currently being evaluated in a phase 1/2 study in pregnant women in the US, UK, and South Africa, and a phase 2b study in 300 non-pregnant women in the US evaluating co-administration with Tdap. Published data from a first-in-human study

showed the vaccine was well tolerated in healthy adults and elicited robust immune responses across all dose levels with and without aluminum adjuvant.[40] Despite this lack of adjuvant effect in non-pregnant adults, adding an adjuvant could potentially change the IgG subclasses produced and increase placental transfer when administered to pregnant women. Evaluation in pregnant women in the phase 1/2 study has demonstrated antibody responses across all serotypes, with similar responses to those seen in non-pregnant women and no advantage of aluminum in terms of antibody levels in seen in infant cord blood. Based on these data, it is likely that the vaccine will have a high degree of efficacy, although results are yet to be published. From a regulatory point of view, the ideal would be that these data could be used as a path to licensure, with a post-approval effectiveness study of the necessary scale used to confirmed effectiveness, although this route is yet to be confirmed.

GBS SEPSIS DURING THE PANDEMIC IN SPAIN

Dr Concepción de Alba Romero, a pediatric doctor and member of the Neonatal Infectious Diseases Committee in Spain then provided an overview of the impact of the COVID-19 pandemic on rates of GBS sepsis in Spain. She introduced the Grupo de Hospitales Castrillo, a group of 45 neonatal hospitals throughout Spain which have been systematically collecting data about neonatal sepsis, antimicrobial resistance, infections, and other related topics since 1995. Approximately one third of all the live births in Spain occur in hospitals included in the network. In the past 25 years, of the approximately 2.5 million live births in the network, 1014 of early-onset GBS sepsis cases have been identified. Screening-based intrapartum antibiotic prophylaxis (IAP) has substantially reduced the incidence of early-onset GBS from 1.25 per 1000 live births in 1996 to 0.29 per 1000 in 2021. However, there has been a small but not statistically significant increase in cases of LOD during this time period. In 1996, prior to the introduction of IAP, 1 in 2 of every early-onset sepsis case in the network was due to GBS. This dropped to 1 in every 4-5 after the introduction of IAP, with the exception of 2020.

Year	1996	2006	2019	2020	2021
Early-onset sepsis cases, n	172	116	101	103	81
GBS, n (%)	89 (51.7%)	38 (32.7%)	23 (22.8%)	**42 (40.8%)**	30 (37.0%)

While the percentage of women being screened for GBS was similar both before and during the pandemic, there was a significant increase in false negative screening, driven by testing being performed at home rather than by healthcare professionals. Additionally, there were significantly more women with GBS colonization who did not receive IAP (47% vs 14% pre-pandemic) as they arrived at the hospital too late in labor. Administering antibiotics to all women in labor would have potentially reduced the rates of sepsis but given the potential side effects and already high rates of unnecessary usage of antibiotics during pregnancy, this would not have been a positive development on an individual or societal level. She concluded that a GBS vaccine in pregnancy is a necessary development that can help save lives of infants.

CURRENT CHALLENGES OF THE MPOX (MONKEYPOX) VACCINE

Professor Asma Khalil, Professor of Obstetrics and Maternal Fetal Medicine at St George's Hospital, London, UK then outlined the challenges of using a mpox vaccine in pregnant women. Since the beginning of the current outbreak of mpox in May 2022, there have been approximately 77,000 cases reported globally (data as of 1st November 2022). Owing to the speed and spread of the outbreak, it was declared as a public health emergency of international concern by the WHO on 23rd July 2022.

Mpox is usually a mild, self-limiting disease, however, in immunocompromised individuals (e.g., pregnant women/young children), the disease can be more serious and have a higher case fatality rate. In May, relatively little was known about mpox in pregnant women, and an article providing information on how to recognize and treat mpox became the most downloaded article from Ultrasound Obstetrics and Gynaecology Journal in 2022.[41] This article presented evidence about maternal and infant outcomes from mpox, as well as advice on management of suspected and confirmed mpox infections in pregnancy. A recent article included a systematic review of 29 studies looking at pregnancy outcomes across pox viruses (smallpox, mpox, and molluscum contagiosum).[42] While molluscum contagiosum appeared benign, mpox and smallpox show similar outcomes in terms of risk of miscarriage, stillbirth, preterm birth, and vertical transmission, although there were no reported maternal deaths from mpox across studies (and the large confidence intervals should be noted). Data up until the beginning of September 2022 show that of the 52,000 mpox cases reported at the time, 10 had been in pregnant women, with no evidence of severe disease or vertical transmission.[43] These findings may differ from previous case reports as they may involve a different strain, differ in access and quality of healthcare/treatments, and there may be an under-reporting of milder cases in Africa which has skewed the case report data. One possible perinatal infection has been reported in the UK, although the role of mpox in the symptoms is not clear as there was co-infection with adenovirus.[44]

Similarly to the initial advice on treatment of COVID-19 in pregnancy, management of mpox during pregnancy was based on a limited amount of evidence. It included advice on mode of birth, whether infants should be isolated, and breastfeeding during infection. A number of other guidelines, also supported by very limited evidence, were also published around this time and gave often conflicting advice.[41,45-47]

	Khalil et al	Dashraath	CDC	SOGC
Treatment options	C, B, T VIG	T VIG	T (1st line), C, B VIG	C, T VIG
Vaccine	Yes, as PEP	Yes	Yes	Yes, as PEP
Mode of birth	CS	CS not advised	-	CS if lesions
Fetal monitoring	Recommend	Recommend	-	-

C: cidofovir
T: Tecovirimat
B: Brincidofovir

Khalil et al. UOG 2022
Dashraath et al. Lancet 2022
https://www.cdc.gov/poxvirus/monkeypox/clinicians/pediatric.html.
https://www.acog.org/clinical-information/physician-faqs/obstetric-care considerations-monkeypox.
https://www.sogc.org/en/content/featured-news/Interim_Guidance_on_Monkeypox_Exposure_for_Pregnant_People.aspx.

It should be noted that none of the treatment options are licensed for use in pregnancy. Tecovirimat, while not being licensed, has not shown any embryotoxic or teratogenic effects in animal studies, and could potentially be used in pregnancy if required. Cidofovir could be recommended if the pregnant woman is severely ill. Brincidofovir is known to be teratogenic and contraindicated. Vaccinia immunoglobulin, which is derived from individuals who had previously been vaccinated with the smallpox vaccine, is not licensed in pregnancy but given that other immunoglobulins are safe, it could potentially be used during pregnancy if needed.

Current guidelines recommend vaccination of contacts of individuals with mpox, sexual partners of persons with mpox, those at high risk of contracting the infection, and lab/healthcare workers with exposure to orthopox

viruses. Administration of the vaccine up to 14 days post-exposure can also reduce symptoms. However, access to vaccines and local guidance on eligibility for vaccination has been highly variable. Of the available vaccines against mpox, the live replicating smallpox vaccine ACAM2000 is contraindicated during pregnancy due to risk of fetal vaccinia which can lead to preterm birth, stillbirth, neonatal death, and adverse maternal reactions. MVA-BN is a live non-replicating vaccine against multiple orthopoxviruses which has demonstrated 85% effectiveness against mpox and is currently available for use in pregnant women (although not licensed). Data in <300 pregnant women have shown no increase in adverse outcomes, and while it is not known whether it passes into breastmilk it is unlikely as the vaccine virus does not replicate effectively in humans.[48]

As seen with COVID-19, a number of studies have been launched evaluating vaccines/treatments for mpox (e.g., PLATINUM study) where pregnant women have been excluded from participation in line with regulatory guidance. As there are no licensed vaccines, there is an urgent need for a systematic approach to prevent and manage the disease in pregnant women.

IMPRINT FOR MATERNAL IMMUNIZATION

Prof Chrissie Jones, Associate Professor in Paediatric Infectious Diseases at the University of Southampton, UK provided an update on the work of the IMmunizing PRegnant woman and INfants neTwork (IMPRINT). IMPRINT's aims include building an international network of stakeholders who are experts on maternal and neonatal vaccination, to increase awareness and uptake of vaccination, engage with industry via placements for trainees, to provide start-up funding to address prioritize challenges, and to fund post-doc fellowships in LMICs. The network was set up in 2017 and now has 316 members across 51 countries, with approximately equal distribution between LMICs and HICs and across genders. To date, the IMPRINT network has funded 32 grants addressing one of the six main identified challenges: 1. Mechanisms of transfer of maternal antibody via the placenta and breast milk; 2. Effects of maternal immunization on infant immunity; 3. Impact of co-factors on maternal and neonatal immunity; 4. Vaccine acceptance and preparedness for maternal immunization; 5. Vaccine safety monitoring, and 6. Development of methodologies for assessing efficacy in clinical trials. In addition, the network has funded approximately 18 months of post-doctoral fellowships (e.g., projects on comparison of GBS IgG in the UK, Bangladesh, and Malawi; vaccine safety monitoring in rural Uganda), which have aided post-doctoral scientists in LMICs with their research careers.

IMPRINT has also been working on public engagement projects in multiple countries and based on this have now developed a public engagement toolkit to help members design and conduct their own public engagement projects. Examples of these projects include an online game to illustrate the importance of vaccines, a number of animated videos to inform the public about currently available and upcoming vaccines, and a fashion project to highlight the importance of vaccines, particularly during pregnancy.

In addition to public engagement, the network has held a number of webinars providing information on maternal and infant immunization during the COVID-19 pandemic, and have organized skills training for members, including media training, vaccine confidence, and public engagement. Several networking meetings have taken place to encourage collaboration: the next members meeting is 6-7 Feb 2023 in Kingston upon Thames, UK. Membership of IMPRINT is free: www.imprint-network.co.uk/membership.

CEPI'S PORTFOLIO CONSIDERATIONS FOR PREGNANT AND LACTATING WOMEN

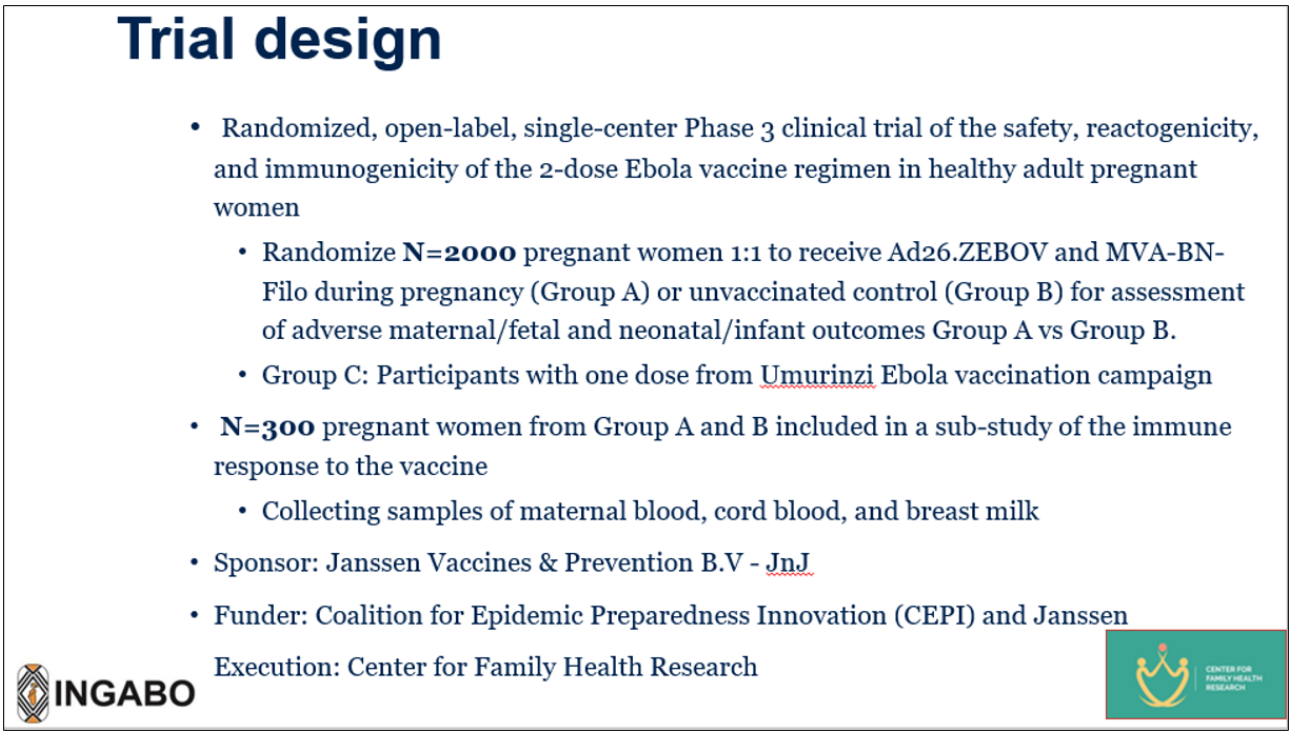
In the final talk of Day 2 Session 1, Dr Gerald Voss, consultant project leader at the Coalition for Preparedness Innovations (CEPI) began by discussing CEPI's vaccine portfolio, which includes 5 candidate vaccines against MERS, 6 against Lassa, 4 against Nipah virus, 3 against Chikungunya, 2 against Rift Valley fever, 11 against COVID-19, and 3 platform technologies against a potential Disease X. Dr Voss highlighted that

immune responses and side effects may vary between vaccine platforms, particularly in special populations (e.g. pregnant women). Therefore, it is essential to maintain a broad portfolio of platforms across candidate vaccines.

CEPI's strategic objectives are based on three main pillars: Prepare, Transform, and Connect. The "Prepare" pillar focuses on developing vaccines and promising biologics against the most prominent known threats, building on the achievements during the first 5 years of CEPI (CEPI 1.0). The "Transform" pillar is mostly focused on Disease X and includes harnessing innovations in technology and systems to significantly reduce the global vulnerability to threats of novel pathogen outbreaks. Finally, the "Connect" pillar aims to connect stakeholders to enable rapid countermeasure development, effective response and equitable access for those in need.

CEPI's aim is to be able to respond to the outbreak of a novel pathogen with a vaccine within 100 days. While this is very ambitious, CEPI uses this aim as a guiding principle and believes it is possible to achieve this vision with strong commitment and collaborations in place. To achieve this, preparedness activities have to be significantly front-loaded, so that vaccine candidates are already available in the event of an outbreak. As part of this preparedness, CEPI aims for timely inclusion of pregnant women in development and implementation of vaccines, as well as creation of a blueprint for expedited evaluation of vaccines during pregnancy. The organization supports key stakeholders in achieving this by facilitating establishment of tools and pathways for inclusion of pregnant and lactating women.

Dr Voss then provided an example of CEPI's support in maternal immunization against Ebola. Ebola in pregnancy poses a high risk, with a case fatality rate of 53–89%, and almost always resulting in a loss of the pregnancy. In the 2018–2020 Ebola outbreak in the Democratic Republic of Congo, pregnant and lactating women were not eligible to receive the 2-dose Janssen vaccine during a mass vaccination campaign (UMURINZI) in neighboring Rwanda. CEPI funded a phase 3 study (INGABO) of the vaccine in pregnant women in the same area which included 2000 participants who either received the vaccine regimen during pregnancy or after delivery. The study also included a third group who had received one dose of the vaccine in the immunization campaign and became pregnant in between the two vaccine doses:



CEPI believes that inclusion of pregnant and lactating women in vaccine development and implementation is an essential consideration to provide timely and equitable vaccine access. The coalition supports stakeholder engagement as well as specific projects, such as the CEPI maternal immunization working group (MIWG) and a workshop of maternal immunization against Lassa fever, which poses a substantial threat during pregnancy. As part of this effort, the MIWG will be an essential resource and forum for the use of both future and existing vaccines during pregnancy and lactation.

SESSION 1 Q&A

1. **Who should be vaccinated against GBS once a vaccine is available?**

   All pregnant women should be vaccinated, as screening is not 100% effective, IAP has not impacted LOD, and colonization can be variable over time.

2. **Is it possible to have a vaccine ready within 100 days?**

   While this was not possible for COVID-19 vaccine development, which was achieved within approximately 9 months, a number of lessons can be learned from this experience which could help with meeting a 100-day target. Firstly, identification of potential pandemic pathogens and development of vaccine components based on related pathogens (e.g., as was done for COVID-19 with MERS and SARS coronavirus spike proteins) could cut timelines for vaccine development once the pathogen emerges. As part of this, virus families could be characterized and stored, with one example per family moved into clinical trials to provide data in advance of emergence of a related pathogen. Additionally, the inclusion of pregnant women in these clinical trials would provide vital data in advance, enabling access to initial vaccine roll-out during an outbreak. Secondly, if immunogenicity data can be used for developing vaccines based on variant strains, timelines could be substantially reduced compared with the need for randomized clinical trials. However, manufacturers also would need to commit to production of vaccines before clear data are available, and therefore would need to potentially manufacture with considerable financial risk. Thirdly, having safety data readily available on vaccine platforms would allow vaccines to be swiftly developed with the emergence of novel pathogens, rather than needing to perform all safety evaluations from scratch.

3. **What are the other potential uses of GBS vaccine, apart from protection against neonatal GBS disease?**

   In the US, GBS is the leading cause of meningitis in under 18 year-olds, therefore a GBS vaccine could be beneficial in reducing the rate of meningitis in older children as well as neonates. In addition, use of a GBS vaccine could provide further insight on the role of GBS in pre-term labor and stillbirth, and potentially reduce these outcomes.

4. **What are the remaining legal challenges to allowing pregnant women to be part of vaccine research?**

   A lot has changed over recent years, with many of the legal hurdles already removed for inclusion of pregnant women in vaccine research. One hurdle which remains is the perception of the theoretical risk of vaccine-related adverse events. Therefore, funding should be allocated to research the potential for these adverse events in general, so that these trials and candidate vaccines are more accessible to women during pregnancy.

SESSION 2: OPTIONS FOR RSV PREVENTION IN INFANTS

RSV VACCINE FOR MATERNAL IMMUNIZATION

Dr William Gruber, Senior Vice President of Vaccine Clinical Research and Development at Pfizer presented an overview of the data from the clinical development of Pfizer's RSVpreF vaccine in pregnant women. RSV remains a significant cause of infant disease globally, with approximately 3 million children under 5 years of age hospitalized each year, and ~150,000 deaths. Until recently, there were no preventative treatments available. Now, palivizumab and nirsevimab, monoclonal antibodies targeting the RSV fusion (F) protein are available in the US (palivizumab) and Europe (nirsevimab and palivizumab) for infants at increased risk of RSV.

Pfizer's RSV vaccine is based on a bivalent stabilized prefusion F-protein and has demonstrated high RSV A and B neutralizing antibody titers in both preclinical and phase 1/2 trials. The F-protein mediates fusion of the virus to the host cell during viral entry and exists as a pre- and post-fusion form. Antibody response against natural infection is mostly directed against epitopes on the prefusion protein,[49,50] and therefore this has been used as the basis for vaccine development as this is expected to elicit a more potent response than targeting elements of the post-fusion protein. Clinical development began with a phase 1/2 first-in-human dose-ranging trial investigating antibody responses to the vaccine with and without adjuvant in healthy adults. Two phase 2b studies then followed, one evaluating safety, immunogenicity, and early efficacy in pregnant women (Savvy study) and one evaluating the impact of co-administration with Tdap in non-pregnant women. The phase 3 pivotal efficacy study (Matisse) is now ongoing in pregnant women aged 18–49 years.

Dr Gruber then outlined the results of the phase 2b proof of concept study in pregnant women.[51] In the study, healthy pregnant women at 24–36 weeks gestation were randomized 1:1:1:1:1 to receive a single dose of one of 4 formulations of the vaccine (120 or 240 µg, with or without alum adjuvant) or placebo. Immunogenicity endpoints included maternal antibody titers at delivery and infant (cord blood) titers at birth. Safety was evaluated throughout the study. Overall, the vaccine was well tolerated with no unanticipated safety findings in the mothers, and low rates of fever. The vaccine elicited robust responses across doses and formulations, with geometric mean ratios (GMRs) >12 at delivery compared with baseline. Antibody responses were maintained post-partum with GMRs of 3.6–5.8 across doses through 6 months after delivery. Titers against RSV A and B were also high in cord blood, with similar antibody responses across formulations. Overall, antibody transfer ratio was similar across Northern and Southern hemisphere countries (which differ in rates of other endemic diseases) and exceeded 1 for all formulations. Antibody titers in infants were still considerably higher than placebo controls at 6 months after birth and were equivalent to those seen for palivizumab. Exploratory estimates of efficacy were 84.7% (95% CI: 21.5–97.6%) against medically-attended lower respiratory tract infections (LRTIs) and 91.5% (-5.6–99.8%) against severe LRTIs.[52]

The Matisse phase 3 study is being performed in 18 countries worldwide and includes approximately 7500 mother and infant pairs randomized 1:1 to 120 µ RSVpreF vaccine or placebo. The study includes women between 24- and 36-weeks gestation and the primary endpoints are RSV-positive medically-attended LRTI or severe LRTI, adverse events from birth to 1 month of age, specific birth outcomes, and SAEs/newly diagnosed chronic medical conditions from birth to the end of the study. Primary endpoint criteria are shown in the table below.

Primary Endpoint Criteria
Medically attended LRTI Medically attended visit and ≥1: • tachypnea (RR ≥60 (<2 m [60 days]) or ≥50 (≥2 to 12 m); • peripheral capillary oxygen saturation (SpO2) measured in room air <95%; • chest wall indrawing
Medically attended severe LRTI Medically attended visit and ≥1: • tachypnea (RR ≥70 (<2 m [60 days]) or ≥60 (≥2 to 12 m); • SpO2 measured in room air <93%; • high-flow nasal cannula or mechanical ventilation; • ICU admission for >4 hours; unresponsive/unconscious

Secondary endpoints for the study include hospitalization rates, all cause medically-attended LRTIs, efficacy against RSV A and B, and efficacy in pre-term

infants (<37 weeks gestation). Mothers are followed up for 6 months post-partum and infants are followed-up to the end of the study. One challenge experienced during the study was the shift in the seasonal pattern of RSV linked to the COVID-19 lockdowns, which have been taken into account with modelling procedures. Interim analysis estimated a vaccine efficacy against severe medically-attended LRTI of 81.8% (99.5% CI: 40.6–96.3%) in the first 90 days of life and 69.4% (97.58% CI:44.3–84.1%) in the first 6 months. Against medically-attended LRTIs, efficacy was 57.1% (99.5% CI: 14.7–79.8%) and 51.3% (97.58%: 29.4–66.8%) in the first 90 days or 6 months of life, respectively. These results met the pre-specified regulatory success criteria for severe medically-attended LRTI indicating clinically meaningful efficacy. The success criterion (lower boundary of CI >20%) was not met for the medically-attended LRTI endpoint withing 90 days, however clinically meaningful efficacy was observed through 6 months. A Biologics License Application (BLA) submission to the US FDA is planned by end of 2022, with additional regulatory authority submissions to follow.

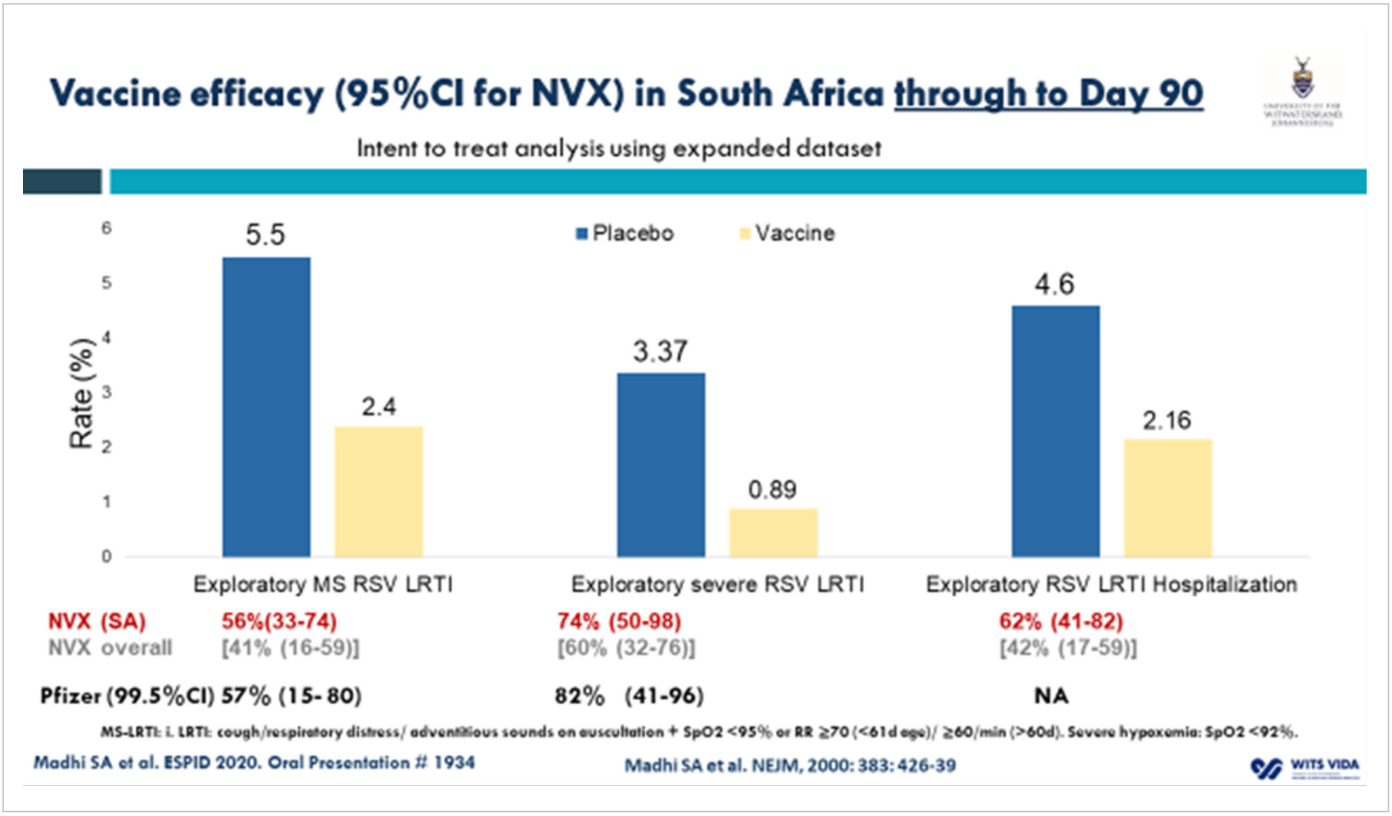
EFFICACY OF NANO-PARTICLE RSV F-PROTEIN VACCINE IMMUNIZATION OF PREGNANT WOMEN AGAINST ALL-CAUSE AND RSV-SPECIFIC LRTI

Prof Shabir Madhi, Dean and Professor of Vaccinology at the University of Witwatersrand, South Africa, provided an overview of data and lessons learned from the PREPARE trial, a global study evaluating Novavax's alum-adjuvanted F-protein nanoparticle RSV vaccine in pregnant women and their infants. The study was performed in 11 different countries and enrolled 4636 pregnant women who were randomized 2:1 to receive vaccine or placebo between 28 and 36 weeks gestation.[53] The primary objective was efficacy against medically-significant (MS) symptomatic RSV LRTI through 90, 120, 150, and 180 days of life in infants (defined as RSV-positive AND ≥1 of SpO_2 <95% at sea level of <92% at >1800m; respiratory rate ≥70bpm in infants 0–59 days of age or ≥ 60bpm in infants ≥60 days of age; AND ≥1 manifestation of LRTI). Secondary endpoints were RSV LRTI with hospitalization and RSV LRTI with severe hypoxemia. Safety assessments were performed through 6 months post-partum in mothers and through 1 year in infants. Exploratory analysis was also performed on an expanded data set including data from sites and hospitalization records.

Unfortunately, the study did not meet its primary endpoint, with estimated vaccine efficacy of 39.4% against RSV-positive MS-LRTI. The overall vaccine efficacy was 44.4% and 48.3% for secondary endpoints of RSV-positive LRTI hospitalization and severe hypoxemia, respectively. In prespecified exploratory objectives, which included RSV-confirmed cases tested for as part of standard of care but in which samples were unavailable for testing at the study central laboratory, vaccine efficacy ranged from 41% of RSV-MS-LRTI to 60% for RSV-LRTI with severe hypoxemia.

In addition, there was a 31% reduction against all cause medically-significant LRTI, and a 44% lower-risk of all cause LRTI hospitalization. Interestingly, there was also a 51% lower risk of all-cause SAE pneumonia from 181–364 days, although the mode of action in preventing this is currently unknown.

Dr Madhi then described post-hoc analysis performed on data from participants in South Africa only (approximately 52% of the study population), which included the extended data set based on cases diagnosed/evaluated by non-study staff. The rate of medically-significant LRTI in placebo-recipients in South Africa was higher than for the overall study (5.5% vs 3.9%, respectively). Many demographics of South African participants differed to those enrolled in HICs; these included race (South Africa: 76.4% Black, HICs: 76.3% White), percentage with children <5 years of age in the household (South Africa: 32.7%, HICs: 22.8%), and percentage of women receiving the vaccine ≥30 days before delivery (South Africa: 88.1%; HICs: 0%). Overall, immune responses in women were similar between South Africa and HICs, but anti-F IgG was lower in infants in South Africa than those in HICs. GMRs of antibody titers were lower than those seen for the Pfizer vaccine, with GMRs of approximately 3 for RSV A and B. Cord to maternal GMT ratio was <1 for both RSV A and B, which is consistent with previous findings for other antibodies seen in studies in South Africa. Overall, vaccine efficacy estimates in South Africa through to Day 90 were higher than for the overall population (56–74% across endpoints) and were more similar to those seen for the Pfizer vaccine than those estimated for the entire study population.



Efficacy estimates to Day 180 were similar to those at Day 90, although very few extra cases were reported between Days 91 and 180. When GMTs were evaluated over time, there was very little difference between the vaccine and control group by Day 90, resulting in half-life estimates of 30.7 for RSV A and 27.0 for RSV B. Therefore, it is expected that in real-world situations in similar settings there would not be significant protection after Day 90.

From a public health point of view, the estimated vaccine efficacy translates to needing to vaccinate ~32 women to prevent a single case of medically-significant LRTI, and 40 women to prevent a single case of LRTI with severe hypoxemia. Overall, only 25, 28, and 32 women would need to be vaccinated to prevent a single case of all-cause medically-significant LRTI, hospitalized LRTI, and LRTI with severe hypoxemia, respectively.

UPDATE ON MONOCLONAL ANTIBODIES FOR RSV PREVENTION IN INFANTS

Dr Octavio Ramilo, Chief of the Division of Infectious Diseases at Nationwide Children's Hospital, then concluded the presentations with an update on the use of monoclonal antibodies for prevention of RSV.

He first described the rationale for the use of passively administered antibodies in infants. RSV varies greatly in terms of clinical presentation from a mild cold to severe LRTI requiring ICU admission and can vary in speed of onset. This variation can be explained by a complex interplay between the virus and the host; viral load does not necessarily correlate with severity, but the age of the host seems to play a key role.

In a study of anti-RSV IgG in patients ≤4 months of age with acute infection, preF antibodies were the most abundant, with a 3-fold increase compared with postF and a 30-fold increase compared with G.[54] Antibody concentrations and neutralizing activity were inversely correlated with age, and higher concentrations of preF and G antibodies (but not postF) were associated with lower severity of clinical disease. In addition, a study

performed in Finland showed that higher titers of maternal RSV preF antibodies in the first trimester was associated with a lower risk of severe RSV disease in infants born to those mothers.[55]

Transcriptome analysis has shown that RSV produces a very distinct profile, which has been validated across separate cohorts.[56] The molecular distance to health (MDTH) score, which is calculated based on the fold-differences in expression across differentially expressed genes for RSV vs healthy controls, has been shown to be correlated with RSV disease severity, including length of hospitalization and days of supplemental oxygen. Therefore, the disease severity is linked to the degree of immune dysregulation. A separate study has also investigated the association between gene expression and disease severity in children of different age groups. In patients aged 0–6 months, severity is driven by inflammation genes, whereas in the 6–24 month group, there is a significant role of interferons (IFN) in modulating severe disease, as children with mild disease showed increased expression of IFN suggesting a protective role of IFN on RSV disease severity (but only after 6 months of age).[57] Transcriptome analysis of healthy infants shows age-dependent gene expression profiles, with under-expression of many genes associated with the innate immune response (IFN, inflammation) and B cells in infants <6 months, and overexpression of T cell responses. A separate study has shown that before the age of 5 months antibody production against RSV is not substantial. Therefore, a strategy concentrating on maternal vaccination and passive immunization through antibody transfer is more likely to be effective than vaccinating very young infants.

Dr Ramilo then briefly described the history of anti-RSV monoclonal antibody development. The first monoclonal antibody was palivizumab, which is a human-derived monoclonal antibody. From this, Motavizumab was developed then developed from palivizumab, based on 13 amino acid substitutions. This antibody demonstrated an increased potency but failed to get approval owing to the rates of skin reactions in clinical trials. The new generation of monoclonal antibodies, nirsevimab and clesrovimab, target preF and have increased potency and longer half-life compared to palivizumab and motavizumab. In the MELODY study, nirsevimab showed 76–79% efficacy vs placebo through Day 151 against medically-attended RSV LRTI, medically-attended RSV LRTI with hospitalization, and very severe medically-attended RSV LRTI, with a good safety profile. When the data from the MELODY study were combined with those from participants receiving the same dose in a phase 2b study, efficacy through Day 151 was even higher, ranging from 79–86.2%. Efficacy against RSV A and B was similar (78.1% and 80.0%, respectively). Neutralizing antibody levels in children treated with nirsevimab were substantially higher than those from natural infection, and did not differ between those who did and did not get infected with RSV.[58] For clesrovimab, pharmacokinetic data in infants indicates that the drug has an extended half-life in pre-term and full-term infants, with a mean of 42 days. Based on data from a phase 1b/2a study, efficacy has been estimated at between 74.2% and 80.6% against medically-attended LRTI (for combined doses and 100 mg only, respectively).

Finally, Dr Ramilo discussed the potential for emergence of resistance mutations. The potential for resistance was noted in a study of suptavumab which appeared to not have efficacy when evaluated against RSV A and B combined, but further analysis showed that the drug only displayed neutralizing activity against RSV A and not against the circulating RSV B strain.[59] A recent study on resistance to nirsevmab through 150 days post-dose showed that very few substitutions in the nirsevamab binding site occurred with >5% frequency during the phase 2b and MELODY studies. Therefore, the likelihood of resistance mutations arising appears small based on this initial study.

PANEL DISCUSSION 1

Dr Janet White, Portfolio and Platform Lead at the Bill and Melinda Gates Foundation moderated the first of the panel discussions. Panelists for this session were Dr William Gruber; Dr Chrissie Jones; Prof Asma Khalil; Dr Octavio Ramilo; Dr Katerina Song; Dr Gerald Voss; Prof Shabir Madhi; Dr Karen Bok, from the National Institute of Allergy and Infectious Diseases (NIAID); and Prof Kirsty Le Doare, Professor of Vaccinology and Immunology at St George's University, London. All meeting participants were invited to contribute to the panel discussions, in addition to the panelists.

The following topics were discussed during the session:

1. **Preparedness for overcoming regulatory concerns about doing pregnancy studies in a future pandemic**

   In addition to regulators, sponsors and manufacturers need to be comfortable with performing research in pregnant women. Over the past decades, progress has been made towards it becoming more acceptable to include pregnant women in vaccine research. From the experience of the pandemic, pregnant women were included in the first round of vaccinations against COVID-19 based on available general data about vaccines in pregnancy. Ideally, toxicology studies and phase 1 studies in non-pregnant adults need to be ready to go as soon as possible so that a study in pregnant women can be planned. DART studies can potentially be performed pre-clinically, although manufacturers may be reluctant to do this for every potential candidate due to financial risk. In addition, as seen during COVID-19, vaccines without specific data in pregnancy will be used in the field in an emergency situation and people are becoming more comfortable with this situation. As seen in the COVID-19 pandemic, there was still a study set-up time of up to 6 months and this should be considerably shortened by proactive planning. The potential for use of existing birth registries and maternal health surveillance in actively facilitating inclusion of pregnant woman was also mentioned, however, many of the clinical trials for emerging infectious diseases are in LMICs which do not generally have comprehensive registries.

2. **How to build and strengthen capacity for sites to conduct clinical trials during pregnancy, particularly in sites in LMICs**

   As has been observed during ongoing clinical trials of maternal immunization, set up and conduct of the trial are easier if sites already have experience of conducting clinical trials, particularly during pregnancy. While maternal immunization has generally focused on infant outcomes, and therefore trials have been led by pediatricians, obstetricians should participate in the implementation of studies of vaccines which include a component of maternal protection. Experience from conducting drug trials during pregnancy can be leveraged for vaccine trials. Mentoring of personnel running trials is important, as there is a limited number of experts in LMICs.

   Challenges to conducting trials during pregnancy in LMICs include the potential for outbreaks of other diseases or political unrest, both of which would reduce healthcare system capacity. It also needs to be noted, that as well as building capacity within sites to conduct trials during pregnancy, the ethical considerations from a local culture point of view need to be considered. As it is potentially a sensitive topic, strong community engagement may also be needed to increase acceptability and aid in recruitment. This includes education on disease burden versus potential risks from vaccination. Within certain cultures it may not just be the pregnant woman herself who is deciding on whether to participate in a trial but would include other family/society members who also need to be engaged. One particular challenge for maternal immunization studies may be the lack of routine ultrasounds and inaccuracy of gestational age estimation, making it difficult to identify prematurity and the gestational window for vaccination.

3. **Are review boards and ethics committees in LMICs open to permitting maternal immunization trials?**

   In the Africa region, regulators are becoming more willing to share information across authorities, with the possibility of performing collective reviews of the evidence. In addition, the WHO maturity levels are a good tool in strengthening regulatory procedures in LMICs.

4. **Routine collection of specific data in clinical trials to increase acceptability and allow robust comparison with background outcomes data**

   As highlighted during evaluations of COVID-19 vaccines, if specific data are not collected during trials it is difficult to refute links to vaccination (e.g., changes in menstrual patterns). Collecting these types of data routinely in clinical trials may help in public acceptability, as any potential links to vaccination can be robustly evaluated. Cohort matching can also be used to help identify any differences in rates of events, particularly events that are population specific.

5. **Multiple vaccines in pregnancy**

   There are a growing number of vaccines which can be administered during pregnancy, and the need for multiple routine vaccines may not be very acceptable to pregnant women, particularly if they do not understand the potential disease threat to themselves or their infant. Ideally, combination vaccines and coadministration should be evaluated, as well as the potential for priming of non-pregnant women where antibody titers can be maintained above protective thresholds for multiple decades. Health economic drivers should also be considered, and the potential for combination vaccines which include different vaccine platforms.

6. **Are there certain patients/populations where monoclonal antibodies against RSV may be preferred to maternal immunization, or vice versa?**

   From the clinical data available to date, both monoclonal antibodies and maternal vaccination against RSV are efficacious. In LMICs, choice of treatments may be mostly driven by availability and cost, whereas in HICs monoclonal antibodies may be preferred in certain situations e.g., pre-term birth. Potentially, monoclonal antibodies would not be needed outside the RSV season whereas maternal immunization would be best administered all year round. It should also be noted that efficacy estimates for vaccines may well differ once implemented outside of a clinical trial. For example, in South Africa, approximately 50% of women were ineligible for inclusion in randomized controlled trials due to HIV status or obesity. Therefore, effectiveness may be different in a real-world situation. Estimates for monoclonal antibody efficacy are expected to be more robust as the study populations were more representative of the real-world population.

7. **Why are rates of transplacental antibody transfer lower in South Africa compared with the US?**

   The rates of transplacental antibody transfer observed in the RSV vaccine study were similar to those seen in a GBS vaccine study in South Africa. Independently of HIV infection, hypergammaglobulinemia was noted as a risk factor for reduced transplacental antibody transfer. There is a high prevalence of CMV infection in South Africa, so this may result in a high prevalence of hypergammaglobulinemia.

8. **What is the current knowledge about RSV epidemiology post-COVID-19 restrictions?**

   Contrary to what was seen in 2020–2021, when there was an inter-seasonal summer peak in RSV, the current experience in South Africa is that the RSV season is similar to those pre-2019, both in timing and severity. In the US, the season began earlier than normal and the severity is so far higher, but with the caveat that 2019 was also a severe year. At the moment, the US is predominantly seeing RSV B infections.

PANEL DISCUSSION 2

The second panel discussion focused on implementation of RSV vaccines in LMICs and was moderated by Dr Ros Hollingsworth. Panelists were Dr Bill Gruber; Prof Kirsty Le Doare; Dr Danny Feikin from the Departments of Immunizations, Vaccines, and Biologicals at the World Health Organization; Dr Niranjan Bhat Lead of the Vaccine Impact Research Team at PATH; Dr Jessica Fleming Maternal Immunization Delivery Lead at PATH; Dr Azucena Bradaji from the Barcelona Institute of Global Health; and Prof Esperança Sevene, Associate Professor at the Universidade Eduardo Mondlane Faculty of Medicine, Mozambique.

The topics discussed in this panel session were:

1. **Potential issues**

   It is expected that RSV epidemiology will return to a seasonal pattern following the abnormal patterns seen after lifting of the COVID-19 restrictions. One issue with RSV vaccination is that it is not perceived as such an important issue as other diseases, so it not prioritized by healthcare professionals. Post-COVID-19, the focus is currently on increasing coverage of other childhood vaccinations, which fell during the pandemic, and continuing with the roll-out of COVID-19 vaccines. There is a need to raise awareness of the burden of RSV and highlight the benefits of vaccination at a country-wide level. This should include evaluation of the full public health value of vaccines (e.g., against all-cause pneumonia) and evidence beyond phase 3 studies (e.g., phase 4 impact trials). In addition, support is needed to aid in roll-out of an RSV vaccine in LMICs, such as was done for pneumococcal and rotavirus vaccines, with close collaboration with maternal/child health and epidemiology colleagues.

2. **2. Considerations for implementation of an RSV vaccine in LMICs**

   The focus needs to be on the implementation of vaccination rather than just pharmacovigilance systems. Maternal and child health programs focus on the most common and serious diseases so need to be prepared in advance to include a new vaccine. With the malaria vaccine, a pilot program was used to help inform decision-making and identify needs for a larger scale roll-out. For example, this could be a randomized roll-out, which could help to counter potential confounders and be beneficial for evaluation of vaccine effectiveness in the population.

   At a country level, data are needed on disease burden and severity. LMICs face lots of competing priorities for disease management at a country level, so policy makers and clinical leaders need to have a clear view of the disease burden and potential public health benefits of vaccination.

   A key element of implementation is shortening the timelines from a vaccine being shown to be efficacious and its availability for use in LMICs. Hepatitis B and pneumococcal vaccines faced large delays in roll-out. Regional effectiveness data could help to shorten these timelines. In addition, practical points need to be considered, such as alignment with existing antenatal care and timings of visits. This can also help with vaccine delivery planning, e.g., number of doses per vial.

3. **3. Increasing acceptability**

   Acceptability of a vaccine is based on the perceived disease burden, severity, and impact of vaccination. An absence of data negatively impacts vaccine uptake. For example, common concerns about COVID-19 vaccines included infertility, menstrual irregularity, and delayed menarche and no data were available to refute these claims. Therefore, proactive collection of some of these outcomes is needed so that these can be readily refuted with evidence. In addition, the individual impact of RSV vaccines is smaller than the impact from a public health perspective (e.g., reduction in hospital bed occupancy and reduced antibiotic usage). Public messaging and education of healthcare providers should be framed to highlight the overall public health benefits, not just the reduction of disease burden. PATH and the WHO have been working together to raise awareness of RSV at a global and regional level and have developed a powerpoint presentation which can be used at regional meetings, as well as a full value profile for RSV vaccines which should be published in Vaccine journal by the end of 2022. Qualitative studies can also be performed to help understand the best communication strategies for engagement.

4. **4. Pharmacovigilance**

   In LMICs, pharmacovigilance is mostly based on spontaneous reporting, therefore under-reporting is an issue. The WHO efforts during the pandemic have helped increase rates of reporting, but it may be that these reduce again post-pandemic. Surveillance should include the regional effects (e.g., areas endemic for malaria) and differences in special populations. Overall, there is a need for effective, specialized surveillance systems (e.g., integrated surveillance across respiratory diseases) to gain a clear insight on disease burden and allow robust estimates of vaccine effectiveness. For example, RSV mortality in the African region appears to be low, but this is likely due to under-reporting. Additionally, follow-up of both mothers and infants is needed post-partum (including vaccinated and non-vaccinated individuals), which will need to be considered for surveillance planning.

MEETING CLOSE

Dr Ros Hollingworth then closed the meeting and thanked all the participants. This meeting provided an opportunity to highlight the hard work and commitment of the Maternal Immunization Working Group throughout the recent COVID-19 pandemic to enable the evaluation and utilization of COVID-19 vaccines in pregnant and lactating women. This working group will be maintained and expanded to address the threat of endemic-, epidemic- and pandemic-related morbidity and mortality by ensuring that pregnant and lactating women have timely and equitable access to safe and effective vaccines.

Key messages from the meeting

- Maternal immunization is a key public health strategy to improve maternal and infant health and reduce early life mortality worldwide.
- Pregnant women with COVID-19 were quickly shown to be at increased risk of severe illness and death compared with non-pregnant women. Additionally, COVID-19 during pregnancy was also swiftly shown to be associated with increased risk for adverse pregnancy outcomes, such as preterm birth and stillbirth. However, recommendations for use of COVID-19 vaccines in pregnancy lagged behind those for the general population, primarily due to exclusion of pregnant women from clinical development programs for these vaccines
- The experience and successes of vaccination during the COVID-19 pandemic provide a tremendous and unique opportunity for maternal immunization efforts to continue in the post-pandemic era. Given the ongoing development of new vaccines for use in pregnant women to address other significant threats, such as Respiratory Syncytial Virus and Group B Streptococcus, it is important to learn from the COVID-19 vaccine experience, to ensure these vaccines can be implemented safely, effectively, and promptly, globally
- Vaccines produced with mRNA technology have the potential to increase the options for safe and effective vaccines against more pathogens, including combination vaccines, and allow improved options for the protection of women during pregnancy and infants in early life.
- The lessons learned from the pandemic regarding research, development and implementation of vaccines in pregnancy can be applied to the next generation of vaccines for use in pregnant women.

Attendance data

Total number of registered attendees including speakers and organizers: 479

Total number of registered attendees excluding speakers and organizers: 449

Groups represented: Funders, developers, regulators, universities, and research centers

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