

# CEPI workshop on Maternal Immunization against Emerging Infectious Diseases, London 12-13 February 2020 – Short Report

## EXECUTIVE SUMMARY

The workshop on maternal immunization against Emerging Infectious Diseases (EIDs) was held to review current evidence and generate initial guidance and next steps for CEPI-funded Lassa vaccine projects. The goal will be to ultimately enable the use of these novel EID vaccines in pregnant and lactating women.

Existing experience with maternal immunization, including in low-and-middle income countries (LMICs), holds lessons for future clinical trials against EIDs. Important conclusions from a recent WHO consultation, field experience from The Gambia, and practical case studies underlined the need for the timely consideration of preclinical and clinical data generation including trials in pregnant and lactating women.

A brief update on the current SARS-CoV-2 outbreak emphasized the importance of preparedness against Pathogen X and outlined regulatory considerations for clinical trials (CTs) in pregnant women. Lessons learned from the Ebola outbreak highlighted the challenges leading to the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) recommendation for the use of the vaccine in an emergency setting. The strong rationale to proactively include pregnant and lactating women in the development of vaccines against EIDs was further supported by a review of Lassa Fever epidemiology and the clinical evidence supporting a specific need to protect pregnant women from the increased morbidity and mortality due to Lassa infection.

Several critical enablers for the conduct of vaccine trials in pregnant and lactating women were identified. Experienced panellists provided testimony and practical guidance for the importance of ethical considerations, community engagement and the adequate communication of risks. Early engagement, clear communication and the continued care for the infants were considered as critical to the acceptance of clinical trials in pregnant women.

Breakout sessions provided an opportunity to benefit from the rich and diverse experience of participants with the aim to generate recommendations for next steps towards the inclusion of pregnant and lactating women in Lassa vaccine development. The discussion of technical considerations concluded that Developmental & Reproductive Toxicology (DART) studies are a requirement and may be complemented by non- Good Laboratory Practices (GLP) preclinical studies to address specific questions. . The cumulative safety data from similar vaccine technology platforms targeting other pathogens can potentially be leveraged. But each Lassa vaccine candidate will need a careful and specific risk-benefit assessment, including a tailored preclinical and clinical development plan for evaluation in pregnant and lactating women.

Critical operational prerequisites for CTs in pregnant women include appropriate liability coverage and insurance, experienced staff and adequate capacity to perform pregnancy related assessments and provide care at and after delivery. Baseline epidemiology data should be available on disease burden as well as background pregnancy outcomes in the region.

No consensus could be reached on the minimum clinical data package needed before and optimal timing of CTs in pregnant women. A thorough benefit-risk assessment should guide CT design in pregnant women. There was agreement that vaccination from 2<sup>nd</sup> trimester makes sense to protect the mother and allow transfer of antibodies to the foetus. Safety surveillance of both the mother and the newborn/infant should be ensured and the immunological assessment of newborns could provide important input into the overall benefit-risk analysis for maternal immunization.

The concluding plenary confirmed the need to proactively include pregnant women in the development of vaccines against EIDs. While there are certain general considerations and requirements, it will be important to devise specific plans for each vaccine candidate. These concrete plans will be required for future discussions with regulatory agencies, who expressed a willingness to consider the specificities related to vaccines against EIDs.

## INTRODUCTION

On 12 and 13 February, 2020, close to 60 maternal immunization and vaccine safety experts, regulators, vaccine developers, Lassa Fever experts and investigators from Lassa-affected countries followed the invitation from the Coalition for Epidemic Preparedness Innovations (CEPI) to review and explore the rationale for vaccination of pregnant and lactating women against Emerging Infectious Diseases (EIDs). The aim was to define the evidence needed and identify critical enablers for vaccine development. The workshop was organised by CEPI within the frame of its mission to ensure that vaccines are made available to the populations that need to be protected against EIDs, including pregnant women.

In the opening address, the impact of maternal immunisation (MI) in reducing morbidity and mortality due to infectious diseases in pregnant women and in providing higher chances of survival to infants was emphasized. Although it is recognised that pregnant women need protection against EIDs through vaccination, questions related to how vaccines should be evaluated and how they could be introduced in this population remain. The purpose of the workshop was to contribute to answering these questions.

## DAY 1

### FIRST PLENARY SESSION - EXPERIENCE WITH MATERNAL IMMUNISATION PROGRAMS IN LMIC

This session was introduced through the review of 3 topics:

- **Conclusions of the WHO consultation on maternal immunisation (Dec 2019)**  
The topics reviewed at the WHO consultation, together with outcome of discussions, were summarized. These addressed i) the immune system in pregnancy, ii) the optimal timing of immunization during pregnancy, iii) the vaccine platforms, iv) the consideration of lactating women separately, v) ethics consultation. The imperative for systematic data collection and rapid data sharing was emphasized.
- **LMIC trial implementation perspective**  
An overview of the existing maternal immunisation clinical trial (CT) platform in the Gambia was provided. This platform has been used for vaccine trials in the past and will be used for planned RSV vaccine CTs. The importance of community sensitization, of the capacity of sites to perform assessments related to pregnancy, delivery and safety monitoring and of appropriate investments in human resources for achieving robust safety and endpoint data was highlighted.
- **Selected case studies with relevance to vaccines against EIDs**  
Possible ways to assess the balance of risks (from the vaccine and from the disease) in pregnancy were reviewed on the basis of 3 examples. These were taken from the specific clinical development of an RSV vaccine for MI; the history of the smallpox vaccine, for which a contraindication in pregnancy exists; and from the accelerated clinical assessment of the vaccine against pandemic influenza 2009 H1N1, which remarkably included a CT in pregnant women.

A panel discussion addressed the need to go faster in the evaluation of vaccines in pregnant women, while generating the appropriate evidence (“go fast slowly”). The possibility of early generation of nonclinical reproductive toxicity data was mentioned. It was noted that CEPI is endeavouring to accelerate this process to be able identify and prioritize the best vaccine candidates early.

## SECOND PLENARY SESSION – DEFINITION OF THE MEDICAL NEED AND RATIONALE FOR VACCINATING PREGNANT AND LACTATING WOMEN AGAINST EIDS, WITH FOCUS ON LASSA FEVER

Four presentations were made:

- **2019-novel Coronavirus and regulatory perspective for vaccination in pregnancy**  
A brief overview of current knowledge with 2019-nCoV (SARS-CoV-2) was provided, highlighting that there is today no evidence of a higher risk for pregnant women, and that assumptions are based on previous data from SARS-CoV and MERS-CoV. The general outlook of regulators on drugs/vaccines for use during pregnancy was presented. This highlighted the fact that EU regulation does not exclude pregnant women from clinical trials, and that specific sections of the SmPC are aimed to summarize all available data related to use in pregnant and lactating women.
- **Clinical experience in pregnant women from the rVSV ring vaccination trial**  
Data that informed the SAGE recommendation regarding the use of the rVSV vaccine in pregnant women were presented. These data are now published (Legardy-Williams, 2020). The analysis was based on data from the STRIVE study (ring vaccination trial in Sierra Leone), where 84 women were inadvertently vaccinated in early pregnancy or became pregnant <60 days after vaccination. This analysis provides valuable, although not conclusive, information about pregnancy outcomes after rVSV vaccination.
- **Lassa fever in pregnant women in Nigeria: epidemiology and clinical outcomes**  
An overview of the overall epidemiology of Lassa fever in Nigeria in the past years was provided, showing a steady increase in the number of cases over the last 3 years. Challenges related to the diagnosis, prognosis and clinical management of Lassa fever in pregnant women were highlighted. Severe Lassa fever leads to major obstetric complications and Lassa fever contributes to 12-21% of the overall maternal mortality in endemic areas in Sierra Leone and Nigeria.

## DAY 2

Day 2 started with an overview of CEPI-funded Lassa vaccine candidates. The '5 + 1' candidates encompass a range of technical platforms. CEPI is aiming for accelerated programmes, planning for an early assessment of reproductive toxicity and the timely evaluation of vulnerable populations (children, under 5, pregnant women and immunocompromised people).

Day 2 was then devoted to the assessment by separate working groups of practical aspects of clinical evaluation of vaccines during pregnancy.

## PANEL DISCUSSION - REVIEW OF OPERATIONAL ENABLERS FOR CTS IN PREGNANT

Contributors started with short presentations as outlined below:

- **Ethics**  
The case was made for inverting the 'presumption of exclusion' of pregnant women from evaluation and access to vaccination to a 'presumption of inclusion'. An anthropological outlook on the role of beliefs around reproduction in the definition of an acceptable risk was provided.
- **Community & stakeholder engagement**  
Experience with Malaria research was used to provide insight into how to engage with key players at different levels (e.g. the village, community leaders, medical staff, the women, the individual) to establish trust. The large vaccination study with the Ad26.ZEBOV, MVA-BN-Filo regimen, which is currently ongoing in North Kivu in DRC and includes pregnant women, provides an insight into the perception of CTS by this population. Pregnant women appear eager to receive the vaccine in this study and most are vaccinated in the 3<sup>rd</sup> trimester. It was noted that most women express the expectation that their infant would be taken care of during their first months of life in the frame of the study.

- **Risk communication plan**

The context of a CT is of importance and recognition of relevant background characteristics (e.g. ethnic groups, language, culture, health system organization) is essential to define appropriate targets, routes and content for communication. It is essential to convey the risks related to the disease and to the vaccine and to manage possible medical misinformation appropriately. The specific situation in the Gambia was reviewed, which highlighted the need to develop proper communication and advocacy plans, including waves of communication through several channels, i.e. TV, radio, printed material and traditional communication involving teachers and religious leaders.

The discussion led to the following main conclusions:

- Socializing should start early to present the vaccine, vaccine trials and rationale.
- Communication needs to be pre-planned and social scientists need to be involved.
- Caring for and evaluating the infant after delivery should be considered.
- Equity aspects need to be taken into account.

## BREAKOUT SESSIONS

Four breakout sessions took place, which examined specific considerations for the development of vaccines against EIDs for maternal immunization. The main conclusions of these sessions are summarized below.

### DART REQUIREMENTS

- A DART (developmental and reproductive toxicity) study is a screening tool for detecting potential effects and does not provide solid predictors for use in humans.
- Preclinical requirements to support CTs in pregnant women:
  - A range of preclinical studies are required depending on the vaccine and technology platform.
  - A DART study must be tailored to the specificities of the vaccine and regimen.
- Data sharing for technology platforms:
  - For a new vaccine antigen using a known platform, if the only change is the insert, the case can be made that a new DART study is not required.
  - There may be situations where it may be possible to include pregnant women in the assessment of vaccination without DART data.
- Vaccine formulation is being refined during the course of a clinical development plan. DART data on early formulation may support CT in pregnant women, depending on the situation.
- Every situation is different, and the assessment has to be case specific.

### ASSESSMENT OF LASSA FEVER CANDIDATE VACCINE TECHNOLOGIES

- CEPI supports several Lassa vaccine candidates, which will have to be prioritized based on systematic benefit-risk assessments.
- Relevant parameters to make an assessment of a vaccine candidate include among others: data in pregnancy of the vaccine platform, replication and potential for transplacental transfer and presence in breast milk. Further work by relevant experts to develop and refine these parameters is needed.
- The suitability for use in pregnant women is a consideration to be prioritized.

## OPERATIONAL PREREQUISITES FOR CTS

Regulators need to be approached early and the AVAREF platform provides an opportunity for discussion and for developing the approach.

Imperative prerequisites were identified as:

- Appropriate liability coverage and insurance.
- Availability of baseline assessments data on disease burden and outcome in pregnant women and on background pregnancy outcomes.
- Study staff with previous experience of CTs and, if possible, of CTs in pregnant women.
- Adequate infrastructure and site capacity to perform pregnancy related assessments and provide care at and after delivery.
- A pregnancy safety monitoring plan and infant follow-up.
- Strengthening of DSMBs and Ethical review boards.
- A community engagement plan, including pregnant women and obstetricians.
- A communication plan.

Other aspects seen by the participants as important although not critical were: having a pregnancy registry in place, the ability to incentivize women to register and sustain the interest, laboratory capacity (which can be outsourced).

## CLINICAL DEVELOPMENT, CT DESIGN

There was much discussion about the minimum clinical data package needed before and optimal timing of CT in pregnant women and a final consensus was not reached. It was pointed out that a thorough benefit-risk assessment may only be available from Phase 2a/b onwards. It was specified that pregnancy evaluation could be nested in Phase 3.

Considerations on CT design in pregnant women:

With focus on Lassa fever, as there is significant mortality from Lassa fever in the 1st and 2nd trimester, the following recommendations were made

- Avoid the 1st trimester due to concerns regarding teratogenicity.
- Vaccinate from 2<sup>nd</sup> trimester as this will allow transfer of antibodies to the foetus and protection of the woman in the 3<sup>rd</sup> trimester, which is associated with the highest mortality burden.
- Inclusion of pregnant women with HIV would depend on the epidemiological setting (HIV prevalence).
- Ensure safety surveillance during and after the CT including in the baby, multi stakeholder approach.
- Consensus that it is important to consider the safety (and immunological) assessment of newborns and follow up of infants.

## CLOSURE OF THE MEETING

The need to ensure that pregnant women benefit from vaccination was reiterated. It was highlighted that there is no single path forward and that each maternal vaccination approach must be examined in its specificities. The experience from Lassa fever, the burden of which is a reality for the pregnant woman and for the unborn, is rich in teachings. Regulators are ready to support maternal immunization. A working group for maternal immunisation at AVAREF could be created. AVAREF is open to receiving suggestions and contributions and to potentially look at a new guideline for CT in pregnant women.

## CONCLUSIONS

- There is a strong rationale for inclusion of pregnant and lactating women in the development of vaccines against EIDs.
- Generation of preclinical and clinical data relevant for maternal immunization should be proactively pursued.
- Ethical considerations, community engagement and clear communication are critical enablers for conduct of clinical trials in pregnant and lactating women.
- Preclinical studies (including DART studies) need to be conducted in a timely fashion and technology platforms can potentially facilitate the generation of data. A thorough risk-benefit analysis is critical for each vaccine candidate.
- Experienced staff and adequate capacity to perform pregnancy related assessments and provide care at and after delivery are essential to the conduct of CTs in pregnant women. Safety and immunogenicity assessments of both the mother and the newborn/infant could provide important input into the overall benefit-risk analysis for maternal immunization.

## NEXT STEPS

- Create a working group of external experts operationally supported by CEPI.
- Develop recommendations for vaccine candidates against COVID-19 (pathogen X) as a model for Lassa Fever and other R&D Blueprint priority pathogens.
- Support the systematic benefit-risk assessment of vaccine candidates using standardized methodology, including development of relevant parameters.
- Consider tailored preclinical and clinical development plans for evaluation of vaccine candidates in pregnant and lactating women.

### *Reference*

Legardy-Williams JK, Carter RJ, Goldstein ST et al. Pregnancy Outcomes among Women Receiving rVSVΔ-ZEBOV-GP Ebola Vaccine during the Sierra Leone Trial to Introduce a Vaccine against Ebola. *Emerg Infect Dis.* 2020;26(3):541-548. <https://dx.doi.org/10.3201/eid2603.191018>