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## Meeting report: CEPI consultation on accelerating access to novel vaccines against emerging infectious diseases for pregnant and lactating women, London, 12–13 February 2020

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## ABSTRACT

Infectious diseases may cause serious morbidity and mortality in pregnant women, their foetuses, and infants; the risk associated with any newly emerging infectious disease (EID) is likely unknown at the time of its emergence. While the ongoing SARS-CoV-2 pandemic shows that the development of vaccines against new pathogens can be considerably accelerated, the immunization of pregnant women generally lags behind the general population. Guided by the priority pathogen list for WHO's R&D Blueprint for Action to Prevent Epidemics, this workshop sought to define the evidence needed for use of vaccines against EIDs in pregnant and lactating women, using Lassa fever as a model. Close to 60 maternal immunization (MI) and vaccine safety experts, regulators, vaccine developers, Lassa fever experts, and investigators from Lassa-affected countries examined the critical steps for vaccine development and immunization decisions for pregnant and lactating women. This paper reports on key themes and recommendations from the workshop.

Current practice still assumes the exclusion of pregnant women from early vaccine trials. A shift in paradigm is needed to progress towards initial inclusion of pregnant women in Phase 2 and 3 trials. Several practical avenues were delineated. Participants agreed that vaccine platforms should be assessed early for their suitability for maternal immunization. It was noted that, in some cases, nonclinical data derived from assessing a given platform using other antigens may be adequate evidence to proceed to a first clinical evaluation and that concurrence from regulators may be sought with supporting rationale. For clinical trials, essential prerequisites such as documenting the disease burden in pregnant women, study site infrastructure, capabilities, and staff experience were noted. Early and sustained communication with the local community was considered paramount in any program for the conduct of MI trials and planned vaccine introduction.

**Abbreviations:** DART, Developmental and reproductive toxicology; DSMB, Data Safety Monitoring Boards; EID, Emerging infectious disease; GACVS, Global Advisory Committee on Vaccine Safety; GAIA, Global Alignment of Immunisation safety Assessment in pregnancy; GAPPs, Global Alliance for Preventing Prematurity and Stillbirth; LASV, Lassa virus; LAV, Live attenuated virus vaccine; LF, Lassa fever; LMIC, Low- and middle-income countries; MI, Maternal immunization; PREVENT, Pregnancy Research Ethics for Vaccines, Epidemics and New Technologies; R&D, Research and development; RSV, Respiratory syncytial virus; WHO, World Health Organization.

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## 1. Introduction

The last decade has seen the emergence of new infectious diseases in low- and middle-income countries (LMIC) with devastating effects on pregnant women and their offspring. Although mechanisms exist to accelerate the availability of vaccines against emerging pathogens, access to vaccines for pregnant and lactating women (hereafter referred to as pregnant women) is still deferred, as recently exemplified by Ebola [1] or COVID-19 [2]. The current COVID-19 pandemic, which started following the workshop reported here, highlights the need to consider pregnant women in early stages of accelerated vaccine development. Data on the risks of COVID-19 in pregnancy have been slow to emerge [3], and clinical studies in pregnant women were initiated approximately one year after initial vaccine approval [4].

The specific physiological regulation of the immune system during pregnancy may explain enhanced disease susceptibility in different gestational periods [5], but these immunological modifications do not prevent an effective response to vaccination [6]. This is exemplified by the success of vaccines currently recommended during pregnancy, whether routinely or during outbreaks [7–12], in reducing the mortality and morbidity of the targeted diseases in women and their infants in the first months of life [13–16]. Safety data available to date have not indicated an adverse effect of these vaccines on pregnancy outcomes [17].

The goal of this workshop was to provide initial guidance to ultimately enable fast access for pregnant women to novel vaccines developed in the context of outbreaks due to emerging infectious diseases (EIDs). Discussions built on current maternal immunization (MI) experience and lessons learnt from case studies in LMIC. Using Lassa Fever (LF) as an example of a devastating disease in pregnant women, the workshop looked at practical ways to accelerate vaccine development.

This report summarizes the workshop discussions and conclusions on:

- (1) The public health need for vaccinating pregnant women against EID.
- (2) The impact of excluding pregnant women from vaccine clinical studies.
- (3) The acceleration of vaccine development based on platform technology knowledge and nonclinical and epidemiological data.
- (4) The operational prerequisites, design of clinical trials in pregnant women, and continued vaccine safety monitoring in this population.

Since the time of the workshop, new systematic reviews and data on disease risks and vaccination in pregnancy have been published. Although we acknowledge the new information brought to the field, these are not cited here as they were not available at the time of the discussions.

## 2. Medical need and rationale

The World Health Organization (WHO) Research and Development (R&D) Blueprint team maintains a list of priority pathogens for accelerated R&D in view of their potential to cause a public health emergency and the absence of efficacious drugs or vaccines [1]. Among these, disease caused by the Lassa virus (LASV) differentially impacts pregnant women, highlighting the need for safe and efficacious vaccines.

Outbreaks of LF have occurred in several countries in West Africa with Nigeria suffering the largest disease burden [18]. Lassa

fever disproportionately affects pregnant women, who suffer particularly severe disease presentation and outcome. While the overall case-fatality rate is 1%, increasing to 15% among patients who are hospitalized with severe clinical presentation of Lassa fever [19], a recent study in Nigeria showed a 36.7% mortality rate in pregnant women admitted to hospital with LF [20]. The maternal mortality rate associated with LF was 50.0% in the first trimester, 75.0% in the second, and 18.7% in the third. Overall, deaths attributed to LF accounted for 13.1% of maternal deaths at the study hospital during the study period. The high viral load observed in pregnant women and the high affinity of LASV for the placenta and vascular tissue may explain this high mortality. The similarity of early LF symptoms (malaise, weakness, headache) with pregnancy-associated symptoms and of severe LF symptoms (convulsion, haemorrhage, sepsis) with major obstetric complications can delay or prevent a diagnosis. LF may be a significant, yet hidden, cause of maternal mortality in many unsuspecting communities in Nigeria [20].

## 3. Revisiting the exclusion paradigm

Classically, pregnant women have been excluded from vaccine clinical trials and evaluation of vaccines in pregnant women deferred to after initial marketing approval. In 2014, the Global Advisory Committee on Vaccine Safety (GACVS) of the WHO conducted a comprehensive review of the safety of vaccines in pregnancy, concluding that there was no evidence of adverse pregnancy outcomes from the vaccination of pregnant women with inactivated viral, bacterial, or toxoid vaccines [17]. However, live attenuated viral vaccines (LAV) are generally contraindicated during pregnancy considering the theoretical possibility for the virus to cross the placenta and due to past experience with the live vaccinia (smallpox) vaccine. The latter provides the only historical evidence of a severe adverse effect (foetal vaccinia) after vaccination during pregnancy, which may result, notably, in foetal death or premature birth [21]. GACVS' review of LAV concludes that the contraindication of measles, mumps, and rubella vaccines during pregnancy is purely precautionary.

Except for new vaccines that are being specifically developed for MI, such as those targeting respiratory syncytial virus (RSV) and Group B streptococcus, the assessment of vaccines during pregnancy has yet to be integrated into clinical development [22]. Unfortunately, the presumptive exclusion of pregnant women from early clinical trials triggers an auto-amplifying process: the exclusion from clinical studies and the ensuing absence of evidence on safety and immunogenicity leads to exclusion from vaccination campaigns, which in turn contributes to a lack of data during pregnancy. As clearly stated in the Pregnancy Research Ethics for Vaccines, Epidemics and New Technologies (PREVENT) recommendation, this can be reverted into a presumptive inclusion that would foster, through the generation of adequate data, the evaluation, recommendation, and use of vaccines during pregnancy as medically needed [23].

## 4. Accelerating the development

Development acceleration requires that the potential need for MI against an emerging pathogen is examined from the start. Workshop participants identified three major ways in which the need for MI can be incorporated into vaccine development from the start:

- The selection of the vaccine platform should consider compatibility with administration during pregnancy.

- Developmental and reproductive toxicology (DART) studies in animal models should be performed early if required in a vaccine-specific approach.
- The disease burden and medical need in pregnant women should be sufficiently documented in early development stages.

#### 4.1. Early platform assessment

There was consensus that examining the suitability of a certain platform to allow the use of vaccine in pregnant women should be a priority. Relevant parameters to make an assessment need to be defined. Participants highlighted that any available data related to use in pregnancy with the vaccine platform, whether vaccination in this population was intended or incidental, was informative. Such information should be compiled and assessed [see section 5.3.3]. In the case of a replicating viral vaccine, the potential for transplacental transfer and transfer in breast milk should be investigated. Pathogen-specific safety considerations also need to be considered. Efforts are underway to examine and determine the criteria that would make a vaccine platform suitable for administration during pregnancy, based on systematic benefit-risk assessments across platforms [24].

#### 4.2. Nonclinical data requirements

The primary concern for MI with preventive vaccines is a potential effect of the product on embryo-foetal growth and development. Participants noted that based on International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use S5 guidelines, a range of preclinical studies are currently required [25–28], although these differ by vaccine and technology platform. These include developmental and reproductive toxicology (DART), local tolerance, neurovirulence, and biodistribution studies. Although they are not firm predictors of safety in humans, DART studies have been felt to offer a screening tool for detecting potential developmental toxicities and risks [25]. These studies must be tailored to the specificities of the vaccine and regimen. Data from these studies are generally required before including pregnant women in clinical studies.

Workshop attendees highlighted that data derived from vaccine antigens using the same technological platform may be used to support the nonclinical safety of a newly developed vaccine based on the same platform, and that this may expedite development. For instance, for a new vaccine antigen using a known platform, such as a new insert for a common viral vector, the case can be made that an additional DART study is not required. Another point of discussion was the vaccine formulation to be used in DART studies. Indeed, ongoing work on the vaccine formulation for manufacturing scale-up commonly occurs in parallel with clinical development, leaving unresolved the question of whether DART data on an early formulation could support initiating a clinical study in pregnant women if subsequent changes have been made to the formulation. Consensus was that every candidate vaccine and situation have their particularities and warrant a case-specific assessment. In some cases, it may be possible to expedite development, and vaccine developers should consult with the relevant regulatory authorities early in development to present rationale and data in support of vaccine-specific approaches.

#### 4.3. Disease burden documentation

Before initiating a clinical trial in pregnant women, an accurate picture should be obtained of disease burden in the general population of women of child-bearing age and in the subgroup of pregnant women through solid epidemiological data collection to describe the clinical manifestations of the disease in these groups,

and ideally with age-stratification. In addition, background data on pregnancy outcomes in the country of the trial should be obtained and clear case-definitions for pregnancy and infant outcomes be available. A basis can be those developed by the Global Alignment of Immunisation safety Assessment in pregnancy (GAIA) project [29]. Such documentation will require close partnership with local maternal healthcare and antenatal care structures for data ascertainment.

### 5. Considerations for clinical assessment

The conduct of vaccine clinical trials in pregnant women presents specific challenges, particularly with regards to clinical study operations and communication about the trial to the local community. These considerations complement the reflections of the WHO consultation on LF vaccine development [30]. The scope was large, and proposals and conclusions should be considered preliminary.

The participants highlighted the following key considerations for conducting vaccine clinical trials in pregnant women:

#### Operational prerequisites

- Appropriate liability coverage and insurance must be in place.
- Study staff should have adequate experience of clinical trials in pregnant women.
- The study sites must have capacity to perform pregnancy related assessments and ability to provide care at and after delivery.
- A plan for pregnancy safety monitoring and for infant follow-up must be in place.
- Data Safety Monitoring Boards (DSMBs) and Ethical review boards with strengthened expertise should be commissioned.

#### Engagement and communication

- A community engagement plan and a communication plan must be developed early.
- Regulatory and policy preferences in countries for evaluation and licensure must be considered for designing the clinical study plan in pregnant women.

#### Clinical trial design

- Vaccinating from the 2nd trimester makes sense for both protecting the mother and the foetus.
- The clinical development plan and study design in pregnant women must be vaccine specific.
- An adequate framework for safety follow-up and pharmacovigilance should be developed.

#### 5.1. Operational prerequisites

Participants noted that there is to date no specific guidance for clinical trials in pregnant women and early discussions with regulators will be beneficial to clarify the approach and its ability to meet requirements. The proposed clinical plan should be agreed as early as possible, particularly with regards to the time of assessment in pregnancy within the overall clinical development plan, data that will trigger the recruitment of pregnant women, and study design. While inadvertent vaccination of pregnant women can occur in early stages of pregnancy, there was consensus that prospective enrolment should occur in later trimesters.

Particularly with regards to LF, it was noted that the African Vaccine Regulatory Forum constitutes a suitable platform for discussion and for the development of formal guidance. In the meantime, attendees stressed that the PREVENT recommendations for

the “ethically responsible, socially just, and respectful inclusion of the interests of pregnant women in the development and deployment of vaccines against emerging pathogens” should be referred to when considering the clinical evaluation of a vaccine in pregnant women [23].

From an ethical and legal standpoint, the country and local context must be understood. For instance, the practical aspects of informed consent must be considered to determine who in the community beyond and in addition to the woman herself, whether individuals or constituted bodies, may need to consent to the participation of pregnant women in the study. An anthropological approach may help in that regard. Ethical review boards should have adequate capacity to evaluate the proposed clinical approach and DSMB should be in place. Modalities for reporting adverse events must be clearly defined and awareness of the process among community members ensured. Local legal requirements for a clinical trial insurance and compensation system must be observed.

Evaluating a medical product in pregnant women obviously faces specific infrastructure requirements, for example to ensure capacity for pregnancy diagnosis and follow-up, to carry out blood diagnostic tests and urinalysis, capacity for delivery and assessment of child development. This requires adequate equipment and personnel expertise, which necessitates careful selection of sites and, possibly, long-term investment in infrastructure and training.

## 5.2. Acceptability and communication

Anthropological studies show that evaluating a medicinal product in pregnant women is prone to generating questions and reactions due to beliefs related to reproduction. Discussions and engagement with local communities is therefore of utmost importance and should start early in trial planning. The approach needs to be holistic, to extend beyond the immediate study location and personnel, and to include the community governance structure. Information about the clinical trial should be provided early and attention must be paid to the timely management of rumours and crises. Efficient communication on risks and uncertainties must be developed. Previous knowledge and experience can be leveraged.

Nigeria was used as an example of a diverse country context, where the multiple regions and states display different culture and languages across numerous ethnic groups and have different health system organization. In this country, differences in perception were seen across regions for polio vaccination, which was accepted in the South and encountered resistance in the North. Information on the trial can first target healthcare workers, then be extended to the broader community to convey the risks associated with the disease and those associated with the vaccine. Efficient communication with the government is also key to deliver an objective picture of the purpose and foreseen outcomes of the trial. Communication should be flexible, customised to the media chosen, with relevant content and focus for different target groups. For example, the resistance to polio vaccination could be overcome with the use of visuals of poliomyelitis disease in children, i.e., through a direct and simple communication on the risk of the disease.

An anthropological outlook can help to understand the role of beliefs related to pregnancy, as there is ambiguity with regards to what is an acceptable risk and what is equitable and just in the context of reproductive governance [31]. An anthropological perspective can also help identify key communities, people and groups for engagement.

Conclusions were that socializing should start early to present the vaccine, the clinical study and its rationale; that communica-

tion needs to be pre-planned and social scientists should be involved; and that caring for and evaluating the infant after delivery should be considered.

## 5.3. Clinical trials in pregnant women

### 5.3.1. When to start

Participants attempted to define the clinical data package needed before starting evaluation in pregnant women and the optimal timing of those clinical trials. The first prerequisite is information on the vaccine risk in this population, meaning that relevant nonclinical data have been reviewed and that previous Phase 1 and 2 clinical trials have assessed the vaccine safety and immunogenicity in the non-pregnant population. A thorough benefit-risk assessment may only be available from Phase 2a/b onwards and vaccination during pregnancy could, at the earliest, be assessed from Phase 2b and possibly be nested in Phase 3.

Consensus was not achieved regarding the minimum clinical data package to be available before starting evaluation in pregnant women. Safety and immunogenicity data from at least 100 non-pregnant adult recipients (including non-pregnant women of childbearing potential) during Phase 1 were considered to represent a possible minimum depending on prior experience with the vaccine construct and the epidemic context.

### 5.3.2. Study design

Elements of a standard trial design for evaluation in pregnant women were reviewed starting from previous vaccine maternal immunization studies. Consideration was given to inclusion and exclusion criteria, and more particularly to the stage of pregnancy in which to vaccinate. There was consensus that vaccinating from the 2nd trimester makes sense for both protecting the mother and the foetus as it allows transplacental antibody transfer in the last stages of pregnancy. Although the woman may benefit from vaccination in the first trimester, as exemplified for LF, the first trimester should generally be avoided for clinical trials because of ongoing embryogenesis and higher incidence in that period of naturally occurring poor pregnancy outcomes such as miscarriages.

No prescriptive design for a clinical trial in pregnant women emerged from discussion as this depends on multiple considerations such as the vaccine platform or the stage of development of the vaccine when the trial is envisaged. The development of the pandemic H1N1 influenza vaccine, RSV vaccine, or the Ebola vaccine regimen (with two trials in Africa) provide examples of possible designs and trial sizes that can be adopted based on specific considerations [32,33].

The pandemic H1N1 flu vaccine clinical trial was considered an example of vaccine accelerated assessment for MI in the context of a pandemic [32]. Although this was not a new pathogen and the safety of influenza vaccines has been largely documented in the past, this illustrates the feasibility of the timely evaluation of vaccination in pregnant women. Indeed, in the wake of the 2009 H1N1 pandemic, which disproportionately affected pregnant women, a vaccine was swiftly developed and tested in all age groups and in pregnant women, before deployment to the public in the US. The candidate vaccine was assessed in adults, elderly individuals, and children and in pregnant women in a rapid sequence. This was made possible through fast protocol development and review by ethical review boards, strong support to data analysis, and result reporting [32]. The clinical study enrolled 120 women, 18–39 years of age, in the 2nd or 3rd trimester of pregnancy. The study was able to conclude that the vaccine was generally well-tolerated, the low dose formulation elicited an antibody response typically associated with protection against influenza infection, and efficient transplacental transfer of antibody was documented [32].

The clinical studies conducted in Rwanda with the Ebola 2-dose vaccine regimen provide examples of a study in the general population that recruits pregnant women and of a study specifically designed to assess the vaccine's safety and immunogenicity in pregnant women [34,35]. The Phase 3 and Phase 2b RSV clinical trial provide examples of studies for a vaccine that is specifically developed for MI [33,36]. Of note, the Interdisciplinary Maternal Perinatal Australasian Collaborative Trials Network seeks to improve maternal and perinatal health by promoting well-designed randomised controlled trials and proposes a peer review and assessment of clinical study protocols [37].

### 5.3.3. Safety evaluation and follow-up

Safety surveillance during and after clinical trials in pregnant women was an important point of focus of the workshop. GAIA, established through the Brighton Collaboration, develops guidance, documents, and tools for clinical trials of immunisation in pregnant women, ensuring safety assessment for vaccines for maternal immunisation. The consortium has provided standardized case definitions for key obstetric and neonatal events for safety monitoring of vaccines in pregnant women [29,38]. These can form the basis for safety evaluation of vaccines in any clinical trial for a vaccine against EID. GAIA has also provided general research considerations regarding LMIC [39,40].

Consensus was that a multi-stakeholder approach would be required, with the building of a broad network for pharmacovigilance in pregnant women. The generation of baseline data on pregnancy outcomes (listed as a prerequisite in section 4.3) could be based on historical data in the local hospital or health care settings. Another source could be data from clinical trials with drugs involving pregnant women in the same region, through information sharing. In 2017, the Global Alliance for Preventing Prematurity and Stillbirth coordinated a group of experts to establish a roadmap for monitoring vaccine safety in pregnant women in LMIC, which represents a rich resource that would benefit to the vaccine community [41].

It was also seen of importance to consider the safety and immunological assessment of newborns and the follow up of infants. Even if the immediate aim is the protection of the mother, such as with LF or Ebola, it may be of value to assess the transfer of antibodies at time of birth and their potential impact on the response to infant vaccination. This would contribute to the assessment of the benefit-risk balance of the vaccine. Ideally, the persistence of the immune response beyond pregnancy should be assessed to help determine the need for renewed or booster vaccination during each pregnancy.

Overall, it proved difficult to define a generic minimal clinical assessment package that would fit any vaccine candidate. The clinical development pathway in pregnant women must be tailored to the vaccine specificities, i.e., the platform, the product profile, the target population, taking into account previous knowledge.

## 6. Conclusion

Evaluating new vaccines in pregnancy, even in the face of public health emergencies as seen during LF outbreaks or recently with the COVID-19 pandemic, remains a challenging endeavour and requires evidence-based consideration of benefits and risks in this vulnerable population. The medical rationale for protecting the pregnant woman and her offspring forms the basis for a shift from the 'presumption of exclusion' of pregnant women from evaluation and access to vaccination to a 'presumption of inclusion' in the face of unequivocal epidemiological data. This workshop succeeded in identifying key critical enablers for the development of vaccines against EID in and for pregnant women.

In early stages:

- The gathering of data on disease burden in pregnancy,
- An early assessment of the vaccine platform for suitability for maternal immunization,
- Prerequisite non-clinical toxicology studies,
- Early engagement of regulators would be essential.

During and following clinical trials:

- Having an adequate infrastructure and expertise for clinical trial conduct and safety follow-up,
- Attention to and planning for local communication on the study and its rationale,
- Establishing a pharmacovigilance network for safety assessment after implementation of vaccination of pregnant women will be important.

Consensus could not be reached on all topics, in particular a generic clinical trial design was difficult to identify as there was wide agreement that trials must be tailored to the specific features of the vaccine and its development stage. Support and guidance for vaccine developers and clinical investigators will continue to be developed and experts in endemic countries and regulators will be key partners in the process.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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