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Commentary

Immunization in pregnancy clinical research in low- and middle-income countries – Study design, regulatory and safety considerations

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ABSTRACT

Immunization of pregnant women is a promising public health strategy to reduce morbidity and mortality among both the mothers and their infants. Establishing safety and efficacy of vaccines generally uses a hybrid design between a conventional interventional study and an observational study that requires enrolling thousands of study participants to detect an unknown number of uncommon events. Historically, enrollment of pregnant women in clinical research studies encountered many barriers based on risk aversion, lack of knowledge, and regulatory ambiguity. Conducting research enrolling pregnant women in low- and middle-income countries can have additional factors to address such as limited availability of baseline epidemiologic data on disease burden and maternal and neonatal outcomes during and after pregnancy; challenges in recruiting and retaining pregnant women in research studies, variability in applying and interpreting assessment methods, and variability in locally acceptable and available infrastructure. Some measures to address these challenges include adjustment of study design, tailoring recruitment, consent process, retention strategies, operational and logistical processes, and the use of definitions and data collection methods that will align with efforts globally.

1. Introduction

Immunization during pregnancy is already established as an important public health strategy to prevent maternal and neonatal tetanus and holds great promise to further reduce infection-related morbidity and mortality for other diseases among pregnant women and young infants [1,2]. This is particularly true in low- and middle-income countries (LMICs), where the burden is greatest for vaccine-preventable diseases and access to basic health services may be limited. Pregnant women are at increased risk of certain infectious disease related morbidity and mortality [1,2]. Pregnancies complicated by infection are at higher risk of adverse pregnancy outcomes, including congenital anomalies, spontaneous abortion and stillbirth, preterm birth and low-birth weight [1,2]. Immunization in pregnancy may provide protection against infectious diseases to the mother, her developing fetus and the newborn infant. This is achieved by increasing antibody levels in the mother against particular infections, so that high and protective levels of antibody are transferred across the placenta to the fetus and are retained by the infant during the time of maturation of their immune system. The success of maternal tetanus vaccination demonstrated the proof of this principle and is part of routine care in many countries [1,2]. Influenza and pertussis vaccines are being

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increasingly recommended as an integral part of immunization in pregnancy programs [3]. Examples of candidate vaccines under development which have a specific indication for use in pregnancy include Group B streptococcus, respiratory syncytial virus, cytomegalovirus, hepatitis E and Zika virus.

Despite the potential benefits of immunization in pregnant women, there is still reluctance to offer or accept vaccines and drugs by some health professionals as well as by some pregnant women [4].

A major source of knowledge about the effects of vaccines on pregnancy outcomes is primarily from observational studies as pregnant women historically were excluded from clinical research of vaccines. More recently, however, clinical trials enrolling pregnant women for various vaccines have been performed in the US and worldwide [5]. Reassuring data regarding the safety and tolerability of vaccines in pregnancy has been accumulated from these prospective clinical trials, as well as from retrospective observational studies and pregnancy registries [5].

Prospective studies on vaccine safety and efficacy differ from other types of interventional studies because the enrolled population is typically broad, does not have a defining illness, the outcomes are often uncommon but serious events, and efficacy is usually defined as a biological rather than a clinical response for the vast majority of study participants. These factors lead to relatively large studies with attendant infrastructure, logistical, resource, and analytical needs.

Conducting research in low resource settings is associated with significant challenges and more so when interventional research is being conducted with pregnant women. Here we consider the challenges related to study design, regulatory and evaluation of safety in clinical trials of vaccines in pregnancy.

There are changes seen in the incidence of the disease, recruitment of pregnant women can be challenging with a high dropout rate, unrelated adverse events are common and timelines and the effort for obtaining informed consent and recruitment is often significantly more than what was originally planned for. Additional barriers to conducting clinical research of vaccines in pregnancy, especially in resource limited settings are the absence of baseline data on disease burden and maternal and neonatal outcomes, variable infrastructure and logistical capacity, regulatory inconsistency from one region to another, cultural factors, and overall lack of harmonization and standards for data collection, assessments, and analysis [6–8]. The investigators, research team and sponsors need to be aware of these ground realities and be prepared to be flexible when unpredictable events occur.

2. Product considerations - safety of vaccines

The safety of vaccines administered during pregnancy is a key consideration for pregnant women, healthcare providers, investigators, regulators, ethics committees, vaccine manufacturers, and communities. There is a need for a globally harmonized approach to actively monitor the safety of vaccines used in immunization programs for pregnant women both during the product development and implementation phase [4]. Active post-introduction surveillance of adverse events following vaccination in pregnancy is required to complement pre-licensure vaccine safety assessments and to promote availability of high quality data particularly in the sensitive phase immediately post licensure, where safety concerns are likely to emerge while effectiveness data may only just be coming available.

However, there are barriers to the evaluation of the safety of vaccines in pregnancy in LMICs. There is a lack of standard definitions of maternal and neonatal outcomes, standards for measurement of these outcomes and harmonized study methods [9]. This lack of harmonization is a challenge for the conduct of clinical research and observational studies, generalizability of safety data and strengthening pharmacovigilance programs in LMICs for immunization in pregnancy and merging of large safety data sets. Large multi-location data sets could optimize the evaluation of clinically important adverse events associated with pregnancy (e.g. microcephaly and congenital abnormalities, stillbirth, preterm birth, neonatal infections, abortions, fetal growth restriction, fetal distress etc.) [4,9,10].

Safety assessment of vaccines and drugs utilized in pregnancy require real-time assessment of risk vs. benefit. Baseline outcome rates are a useful part of such an assessment. There is little progress in determining baseline rates in LMIC settings of maternal and neonatal outcomes [4,9–11].

3. Study specific considerations for immunization in pregnancy in LMICs

3.1. General study design considerations

Studies in LMICs need to address a series of typical methodological challenges [12]. For example, baseline incidence rates of pregnancy and neonatal outcomes collected through previous studies or public records inform a series of sample size calculation data. Unfortunately reliable incidence rates of common disease conditions in LMICs are scarce. Public records are often unreliable and inconsistent and are gathered by different agencies at different time points or concurrently, sometimes using different methodologies. It is highly advantageous to determine or validate these background rates in the populations being studied prior to the conduct of the clinical research in that population. Further complicating the scenario is lack of use of standardized case definitions to distinguish conditions like stillbirths from miscarriages and lack of accurate assessment of gestation age [9,12,13].

3.2. Evaluating potential risks and benefits

As a fetus or infant cannot consent to participation in research, a critical issue is how much risk is acceptable to impose upon the fetus or the infant. For research with the potential of direct medical benefit to the woman or fetus, risk proportionate to the potential benefit is acceptable. For research that does not involve the prospect of direct medical benefit, risk to the fetus must be no more than minimal. However, the definitions of minimal risk in the context of pregnancy are unclear [7,12,14].

There is a need to determine adequate methods for estimating incidence rates, testing hypotheses and determining causal associations of the outcomes of vaccination in pregnancy in LMIC [13,15–17] to provide the evidence based reassurance of what are the actual risks from participation in research. An example is that major structural or genetic birth defects affect about 3% of all births in the United States and are associated with 20% of all infant deaths. Accurate collection and ascertainment of birth defects in LMICs is lacking [15]. The causal events of most birth defects are unknown, but some surveys and commentators ascribe participation in research studies or medical interventions as risk factors [17].

3.3. Risk adjusted study design

Researchers need to be scientifically strong, responsible and sensitive to the realities in LMICs while planning research designs which promote inclusion of pregnant women in research. A key consideration is maintaining and effectively communicating maternal and fetal safety. Progressing from healthy adults to

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