STUDY PROTOCOL

Protocol for a pregnancy registry of maternal and infant outcomes in Uganda - The PREPARE Study [version 1; peer review: awaiting peer review]

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Abstract

Background: Pregnancy is associated with complications which must be differentiated from adverse events associated with the administration of vaccines during pregnancy both in clinical trials and post licensure surveillance. The frequency of pregnancy related complications varies significantly by geographical location and the prevalence of pregnancy and neonatal outcomes are poorly documented in most low-resource settings. In preparation for Group B Streptococcus maternal vaccination trials, we describe a protocol for a pregnancy register at Kawempe National Referral Hospital, Kampala, Uganda to describe pregnancy maternal and infant outcomes.

Methods: The study has two components. Firstly, an active, prospective surveillance cohort consisting of pregnant women in their first or second trimester recruited and followed up through their hospital scheduled antenatal visits, delivery and their infants through their extended programme of immunisation visits until 14 weeks of age. Data on obstetric and neonatal outcomes defined by the Brighton Collaboration Global Alliance of Immunisation Safety Assessment in Pregnancy criteria will be collected. Secondly, a passive surveillance cohort collecting data through routine electronic health records on all women and infants attending care at KNRH. Data will be collected on vaccinations and medications including antiretroviral therapy received in antenatal clinic and prior to hospital discharge.

Discussion: Conducting vaccine research in resource-limited settings is essential for equity and to answer priority safety questions specific
to these settings. It requires improved vaccine safety monitoring, which is especially pertinent in maternal vaccine research. During a trial, understanding the epidemiology and background rates of adverse events in the study population is essential to establish thresholds which indicate a safety signal. These data need to be systematically and reliably collected. This study will describe rates of adverse pregnancy outcomes in a cohort of 4,000 women and infants and any associated medications or vaccines received at a new vaccine trial site in Uganda.

**Keywords**
Global Alliance of Immunisation Safety Assessment in pregnancy (GAIA) outcomes, Group B Streptococcus (GBS) vaccine, maternal, neonatal, electronic health records, pharmacovigilance
Introduction
Tremendous progress in child survival has been made over the past two decades globally. However, the neonatal period still represents an extremely vulnerable period. There were an estimated 2.5 million neonatal deaths in 2020 accounting for roughly 47% of all under-five child deaths. Infections are one of the most important causes of neonatal deaths after complications of prematurity and intrapartum events and are a clear focus for reducing mortality. Maternal immunisation offers an attractive public health intervention for reducing neonatal infectious mortality.

Immunisation research in low-resource settings
Maternal immunisation is an evolving field that deserves special attention given its potential to have a significant positive impact on the health of women and children globally, and the potential safety and risk considerations associated with research in this population.

The goal of maternal immunisation is to boost maternal levels of specific antibodies to provide the newborn and young infant with sufficient immunity at birth, through placental transfer in-utero, to protect them through the period of increased vulnerability to infection. The success of the maternal neonatal tetanus immunisation program demonstrates the utility of this approach. Several other vaccines are recommended in pregnancy, including influenza and pertussis. Promising new vaccines for group B streptococcus (GBS), respiratory syncytial virus (RSV) are under development. They are targeted for use in pregnant women in high-, middle-, and low-resource settings. However, these vaccines are likely to be of most benefit in low-resource settings that have high rates of vaccine preventable diseases.

Maternal interventions vigilance (MIV) is challenging as pregnancy itself can be associated with obstetric or fetal events during gestation that carry a risk of complications. Vital registries and health reporting systems for pregnant women and infants are often insufficient in low- and middle-income countries (LMICs), and most existing population-based health surveillance-systems lack the sensitivity needed to track complications of pregnancy and adverse birth outcomes. Even serious adverse events, such as fetal loss, stillbirth, congenital anomalies, and neonatal death, are often not accurately counted, reported, or investigated in many countries. However, these data are crucial for safe implementation of maternal vaccines at all stages from pre-licensure through to implementation.

It is vital that the background rates of pregnancy and neonatal outcomes are clearly documented as these vary by setting, so that safety signals during vaccine trials and in post-licensure surveillance can be correctly assessed. Given the important contribution that maternal immunisations could make to reduce maternal and neonatal morbidity, efforts are underway to standardise case definitions used to classify adverse events in maternal vaccine trials. Historically, this has not been the case, limiting comparability between countries and pre- and post-licensure.

Harmonisation of maternal vaccine safety monitoring
In 2014, in response to a call from the World Health Organisation (WHO) and with funding from the Bill and Melinda Gates Foundation, the Global Alignment on Immunisation Safety Assessment in pregnancy (GAIA) consortium was formed, with the goal of developing a harmonised, globally concerted approach to actively monitor the safety of clinical trials, vaccines and immunisation programs in pregnancy. The group have developed over 25 standardised case definitions for the classification of adverse obstetric and neonatal events including the need to follow-up vaccinated women for six months and infants for one year following vaccination. These case definitions are divided into levels of certainty with greatest specificity at level one (whilst maintaining sensitivity) and decreasing specificity with decreasing levels of certainty (1-3).

We describe a Pregnancy Registry protocol designed to determine background rates of adverse events, including outcomes following tetanus vaccination (the only routine maternal vaccine given in Uganda). The registry is integrated into Ugandan Ministry of Health electronic health records. It is not specific to any vaccinations, so can be adapted as future vaccines are added to the antenatal programme. The registry will build capacity for adverse events following immunisation in pregnancy in low-resource settings to improve maternal and neonatal care and vaccine confidence.

Study aims
This prospective observational cohort study aims to describe background rates of adverse pregnancy and neonatal outcomes at a new vaccine trial site in Kampala, Uganda. Data on these outcomes will be collected from enrolment in antenatal clinic until at least 14 weeks post-partum. Key outcomes of interest have been prioritised based on the GAIA guidelines and case definitions. Field-performance of the novel GAIA case definitions will be assessed.

Study setting
The study is based at a maternity national referral hospital (Kawempe National Referral Hospital (KNRH), Kampala). KNRH is the largest national referral hospital for pregnancies in Kampala, Uganda’s capital city, admitting high-risk pregnancies from surrounding areas and all deliveries from the local community. The neonatal unit admits all preterm infants weighing over 1000g, and neonates with birth-related complications, septis or congenital anomalies (approximately 11,000 admissions per year). There are approximately 25,000 births per year at KNRH.

Protocol – Study design
Component 1
Component 1 aims to describe baseline maternal and neonatal outcomes using anonymised data collected using the routine Electronic Medical Records (EMR) system at KNRH. Ascertainment and under-ascertainment of the EMR system will be described to assess the efficacy of the system in identifying adverse outcomes of pregnancy and infancy. Data on GAIA defined outcomes for all women and babies attending KNRH
for the study duration will be collected and analysed. There is no exclusion and inclusion criteria for this component and mothers and babies will receive no intervention or follow-up.

**Objectives**

1) To describe maternal, obstetric, and neonatal outcomes in the entire population that attend KNRH for antenatal, delivery and/or post-partum care during the two-year study period.

2) To measure ascertainment and under-ascertainment in the hospital EMR system.

3) To assess the level of certainty that can be ascribed to GAIA outcomes in the hospital case files for women receiving routine vaccinations.

**Primary endpoints**

1) Maternal, neonatal, and infant adverse outcomes captured in EMR.

**Secondary endpoints**

1) Maternal, neonatal, and infant in-hospital mortality captured in EMR.

2) Proportion of PREPARE cohort with GAIA adverse events of interest, accurately captured within the KNRH EMR system.

3) Proportion of the adverse events (such as stillbirths, neonatal deaths, caesarean sections, hypertensive disorders etc.) from the hospital registers captured in EMR.

**Exploratory endpoints**

To assess the level of certainty with which obstetric and neonatal outcomes can be defined using GAIA definitions.

**Data collection and management**

Mother and infant data will be collected and entered into the EMR systems maintained at KNRH. Study staff will ensure complete and accurate data are collected and entered into the EMR system. The primary health provider information on the participant’s hospital medical records is the source information. The data collected will include: maternal age, parity, gravida, complications in pregnancy (gestational diabetes, placenta previa, autoimmune disease, preeclampsia), Human Immunodeficiency Virus (HIV) status, past medical history, medications, vaccines received, complications in the peripartum period (eclampsia, maternal infection, obstructed labour, post-partum haemorrhage, etc.), mode of delivery, birth outcome (term, preterm, still or livebirth), gestational age (the GAIA algorithm for gestational age assessment will be used), infant birth outcomes (asphyxia, congenital abnormalities, microcephaly, etc.), acute admissions, neonatal sepsis, and neonatal encephalopathy. De-identified study participant EMRs will be exported to a study database using a unique study ID number. No identifying information will be stored in the REDCap study database.

Data on GAIA outcomes will be collected at screening in the antenatal care (ANC) visits, follow-up visits, at delivery and during post-natal or Extended Program of Immunisation (EPI) visits.

The KNRH registers will be used to count the number of events of interest (stillbirths, neonatal deaths, caesarean sections, hypertensive disorders etc.) recorded per week. The number recorded in the registers will be entered into a REDCap study database along with the numbers captured in EMR to generate a proportion captured.

Participants with the GAIA adverse outcomes will be identified by the Data Manager and their hospital ID numbers shared with the KNRH EMR team via password protected document only accessible to the staff member reviewing EMR. The EMR team will confirm if the event was captured in the EMR system or not and enter anonymised data into the REDCap study database.

**Component 2**

Component 2 aims to collect comprehensive data on pregnancy and infant outcomes in a prospective cohort of 4,000 women enrolled during their first or second trimesters while attending ANC at KNRH and will follow-up the mother and infant/s up until 14 weeks post-partum. The population reflects women eligible for inclusion in a pregnancy vaccine trial and will assess the suitability of using data collected in component 1 to inform and design future clinical trials. Women will be assessed for eligibility and potential participants will be recruited after a routine pregnancy dating ultrasound scan that will be offered to pregnant women attending ANC at KNRH.

**Objectives**

1) To determine baseline pregnancy and neonatal outcomes (Table 1) among pregnant women enrolled in the first or second trimester of pregnancy attending ANC at KNRH.

2) To determine baseline maternal, neonatal and infant (up to nine months) survival rates in an active cohort receiving routine immunisations.

3) To assess field-performance of the GAIA definitions in this cohort.

**Primary endpoint**

1) Incidence rates for obstetric and neonatal adverse outcomes.

**Secondary endpoints**

1) Maternal mortality rate during pregnancy and until 14 weeks post-partum.

2) Neonatal mortality rate (death within the first 28 days).

3) Infant mortality rate (up to nine months).

4) Maternal and infant immunisation rates.
Table 1. Published GAIA case definitions.

<table>
<thead>
<tr>
<th>GAIA outcome</th>
<th>Focus</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth</td>
<td>Neonate</td>
<td>2016</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>Neonate</td>
<td>2016</td>
</tr>
<tr>
<td>Maternal death</td>
<td>Pregnancy</td>
<td>2016</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>Neonate</td>
<td>2016</td>
</tr>
<tr>
<td>Congenital microcephaly</td>
<td>Neonate</td>
<td>2017</td>
</tr>
<tr>
<td>Fetal growth restriction</td>
<td>Pregnancy</td>
<td>2017</td>
</tr>
<tr>
<td>Non-reassuring fetal status</td>
<td>Pregnancy</td>
<td>2016</td>
</tr>
<tr>
<td>Antenatal bleeding</td>
<td>Pregnancy</td>
<td>2017</td>
</tr>
<tr>
<td>Dysfunctional labor</td>
<td>Pregnancy</td>
<td>2017</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>Pregnancy</td>
<td>2017</td>
</tr>
<tr>
<td>Hypertensive disorders in pregnancy</td>
<td>Pregnancy</td>
<td>2016</td>
</tr>
<tr>
<td>Pathways to preterm birth</td>
<td>Pregnancy</td>
<td>2016</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>Pregnancy</td>
<td>2017</td>
</tr>
<tr>
<td>Ectopic Pregnancy</td>
<td>Pregnancy</td>
<td>2017</td>
</tr>
<tr>
<td>Postpartum haemorrhage</td>
<td>Pregnancy</td>
<td>2016</td>
</tr>
<tr>
<td>Neonatal encephalopathy</td>
<td>Neonate</td>
<td>2017</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>Infant</td>
<td>2017</td>
</tr>
<tr>
<td>Low birthweight</td>
<td>Neonate</td>
<td>2017</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>Neonate</td>
<td>2016</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>Neonate</td>
<td>2017</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>Neonate</td>
<td>2017</td>
</tr>
<tr>
<td>Neonatal infections</td>
<td>Neonate</td>
<td>2016</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>Pregnancy</td>
<td>2019</td>
</tr>
<tr>
<td>Neonatal seizures</td>
<td>Neonate</td>
<td>2019</td>
</tr>
<tr>
<td>Neurodevelopmental delay</td>
<td>Infant</td>
<td>2019</td>
</tr>
<tr>
<td>Postpartum endometritis</td>
<td>Pregnancy</td>
<td>2019</td>
</tr>
</tbody>
</table>

**Exploratory endpoints**
- Predictive value of the case definitions (compared to expert panel case file review).
- Factors associated with adverse maternal and infant outcomes.
- Adverse events following tetanus or tetanus-diphtheria vaccination.

**Inclusion criteria (Component 2)**
Inclusion criteria for pregnant women are:
- Able and willing to provide written informed consent to take part in the study.
- ≥14 years of age
- Presenting in first or second trimester of pregnancy as defined by either: Abdominal US (USS), last normal menstrual period, or fundal height measured in centimeters.
- Planning to attend for ANC and delivery at KNRH.
- Planning to stay within Kampala or nearby Wakiso district until the infant is at least nine months’ old.
- Willing to attend immunisation visits at six weeks following the end of the pregnancy and end of follow-up visit (at 14 weeks or nine months) at KNRH.
- Willing to be contacted by phone and/or be visited at home.

Inclusion criteria for their infants are:
- Has written informed consent provided by parent(s)/guardian to take part in the study.

**Sample size considerations**
A post-hoc analysis of data collected during a prospective observational cohort study (ProGreSs study)13 and KNRH hospital level denominator data was conducted to estimate the crude background rates of adverse outcomes at the Kawempe Hospital site. These demonstrated that stillbirth occurred in the range of 1.0–4.3% of births, prematurity in 6.6–10.7% and maternal deaths in 0.1–1.0%.

With a sample size of 4000 participants on an observed incidence proportion of 1% (the minimum estimate of stillbirth rate), we would observe an absolute precision of 0.36% with a 95% confidence interval (two-sided). For a more common outcome such as prematurity (7–11%), we would observe an absolute precision of +/- 0.9% (Table 2). This sample size was therefore estimated to be both feasible in terms of recruiting this number of participants from ANC over the course of the study and sufficiently precise.

**Study procedures**

**Screening and enrolment**
Women will be assessed for eligibility when they attend routine ANC. Pregnant women will be referred for study enrolment by their antenatal primary care providers. On referral, study staff will provide information about the study. Those women interested will undergo an informed consent process and be assigned a participant identification number if they agree to participate. All women enrolled from antenatal clinic will have a sticker placed on their hand-held notes they carry to subsequent appointments and delivery, and the same sticker will be placed on the case file or study card maintained by study team staff in order to help identify participants. Baseline demographics and past medical history will be recorded in an electronic case report form (eCRF). All women will be screened for HIV and syphilis on recruitment as part of routine care. Any woman with a positive result will be referred for appropriate care. Details of any adverse outcomes, medications or vaccinations will be recorded at enrolment and subsequent visits (Figure 1). Study-specific staff
Table 2. Precision around point estimates based on 4000 sample size.

<table>
<thead>
<tr>
<th>% with outcome</th>
<th>Lower limit of the 95% CI</th>
<th>Upper limit of the 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1%</td>
<td>0.03</td>
<td>0.26</td>
</tr>
<tr>
<td>1%</td>
<td>0.72</td>
<td>1.36</td>
</tr>
<tr>
<td>2%</td>
<td>1.59</td>
<td>2.48</td>
</tr>
<tr>
<td>3%</td>
<td>2.49</td>
<td>3.58</td>
</tr>
<tr>
<td>4%</td>
<td>3.41</td>
<td>4.65</td>
</tr>
<tr>
<td>5%</td>
<td>4.35</td>
<td>5.72</td>
</tr>
<tr>
<td>10%</td>
<td>9.09</td>
<td>10.97</td>
</tr>
<tr>
<td>15%</td>
<td>13.91</td>
<td>16.14</td>
</tr>
<tr>
<td>20%</td>
<td>18.77</td>
<td>21.27</td>
</tr>
</tbody>
</table>

Figure 1. Study visits and surveillance outcomes.

Active Surveillance for:
Obstetric Outcomes
- Spontaneous abortion & ectopic pregnancy
- Gestational diabetes
- Hypertensive Disorders of pregnancy
- Antepartum haemorrhage
- Fetal growth restriction
- Pathways to preterm labour
- Non-ressuring fetal status
- Dysfunctional labour
- Post-partum haemorrhage
- Maternal death
- Chorioamnionitis

Neonatal outcomes
- Preterm birth
- Stillbirth
- Low-birthweight
- Neonatal sepsis
- Neonatal encephalopathy
- Neonatal death
- Respiratory distress
- Neonatal infections

Infant Outcomes
- Failure to thrive
- Infant death

Surveillance for adverse events

Labour and delivery
Participants will be seen on the labour ward by study staff. Mother and newborn/s will be evaluated at birth and prior to discharge. Condition at delivery including live or stillbirth, APGAR scores, birthweight and presence of congenital abnormalities will be recorded. Babies will have a Ballard score assessment of gestational age performed by trained staff. Babies requiring admission to the neonatal unit will have details of this admission recorded. Babies will receive a Bacillus Calmette–Guérin immunisation at birth from the hospital team as per the Ugandan EPI schedule.
Telephone follow-up
A telephone call will be made to the participant within 28 days of the end of the pregnancy to check on the wellbeing of the mother and infant/s (if liveborn).

Routine immunisation visits
The participant, their hospital records and mother and baby passports (if liveborn) will be reviewed at EPI visits if the mother chooses to seek care at the KNRH EPI clinic. (https://www.unicef.org/uganda/key-practice-immunization).

If participants choose to have routine visits at an alternative site, then details of the immunisation history and record of the attendance will be retrieved from the mother and baby passport, other medical documentation, or verbal history during the next enhanced visit to KNRH.

Enhanced visits
All participants with infants will be asked to have their six-week and final immunisation visits (14 weeks and nine months) at KNRH. Details of any hospital admissions and the baby’s growth (length, weight, examination findings of malnutrition) will be recorded.

Visits for women that have stillbirths/abortions/neonatal deaths
Study participants that deliver stillborn infants, have a spontaneous abortion or whose babies die, will receive a telephone call or home-visit to provide psychosocial support where possible. They will undergo follow-up at six weeks and either 14 weeks or nine months by telephone, home-visit or KNRH attendance to check on their health and to record any complications experienced following the end of the pregnancy.

Missed visits
In cases where protocol-defined visits were missed because the mother decided to seek care in an alternative location, a member of the study staff will contact the participant to check on their health status by telephone and/or home-visit.

Recording admissions/deaths
The participant will be asked to contact the study staff if their infant becomes unwell, is admitted to a health centre or hospital, and/or dies. If either the mother or infant is unwell, they will be encouraged to attend KNRH to be cared for by medical staff. Details of any attendance or admissions will be captured by study staff.

Maternal deaths
If a mother dies during the course of the study and the infant’s father had not given consent at enrolment, then the infant’s guardian will be asked to provide written informed consent for the continued participation of the baby. If written informed consent is not given the infant will be withdrawn from the study.

Duration of participation
All mothers and infants will be followed-up from the date of enrolment until at least 14 weeks post-partum. Participants who deliver early in the recruitment period (at least nine months before the end of the study) will be followed-up until completion of their EPI visit at nine months. Participants enrolled with fewer than nine months of the study remaining will have their final study visit at the 14 weeks EPI visit.

Data analysis
Adverse outcome incidence rates
We will describe the characteristics of the cohort of mothers and infants. Continuous variables will be summarized using means, standard deviations, medians and ranges based on the normality assumption. Categorical variables will be summarized using proportions and exact (Clopper-Pearson) intervals. Incidence rates will be presented as point estimates with their 95% confidence intervals. We will estimate rates of adverse pregnancy outcomes including stillbirth, premature births and maternal deaths as well as neonatal mortality, maternal mortality and infant mortality according to the relevant data collection time points (i.e., 28 days, 14 weeks or nine months post birth). Survival analyses may be explored for outcomes that occur at later timepoints.

Field-performance of case definitions
The GAIA case definitions are classified by levels of certainty (Table 3). Data entered in the eCRFs will be classified according to whether there is sufficient information to define the event as a case. For reported events with insufficient evidence, an expert medical panel, consisting of at least one specialist (obstetrician or paediatrician) and at least one other medical practitioner, will review the medical notes to determine whether it is a case (level 4) or not (level 5). The sensitivity, specificity and predictive values of the case definition compared to expert medical panel will be considered.

Factors associated with poor outcomes
Multivariable regression methods will be applied to assess rates of adverse pregnancy and neonatal outcomes separately. Maternal factors may include age, HIV status, syphilis, Hepatitis B disease, LMP, maternal comorbidities, parity and antenatal history, vaccinations and medications received. Infant factors may include sex, gestational age, birth weight, condition at birth, and admission to the special care baby unit. Other potential relationships may be considered.

Data management
A dedicated clinical data management system (CDMS) project for screening and enrolment visit data that contains personal identifying information and protected health information will be created in Open Data Kit (v2022.2.2) to reproduce the screening and enrolment eCRFs. Only individuals that are part of the study team, the sponsor team, quality management team, the affiliated reviewers or auditors will be given access to the study data collection systems and study data, all databases will be password protected. Paper consent forms will be kept in a locked filing-cabinet within a locked study office at KNRH and transferred regularly for secure-storage at the research centre.

Electronic case report forms (eCRFs) will reflect the visit schedule and all subject related data to be collected, as
Table 3. GAIA case definition levels

<table>
<thead>
<tr>
<th>Event meets case definition:</th>
<th>Reported case with insufficient evidence to classify</th>
<th>Not a case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1: Criteria as specified in the CD</td>
<td>Level 4</td>
<td>Level 5</td>
</tr>
<tr>
<td>Level 2: Criteria as specified in the CD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 3: Criteria as specified in the CD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

described by the study protocol. Within the database, coded values will be used in preference to free text values, and automatic score calculations will implemented, where appropriate. The eCRFs will apply logical and managerial controls over data capture in order to ensure consistency, completeness and validity. The study staff will enter the data in the eCRFs contained within the data collection systems using the contents of the participant’s KNRH hospital records/other medical records. Study staff will use computer tablets to access the study CDMS through a web browser. The data centre has eight physical and over 25 virtual servers and core networking equipment all running off uninterruptible power supplies and supported by two backup generators (primary and secondary) with an active phase failure warning system in case of power line failure. All data will be held on these secure servers that are backed-up daily.

Quality control (QC)

eCRFs will be programmed with real-time validation checks to alert data entry users to missing data, check numeric variables and dates are within ranges and check for consistency across the data.

Quality control (QC)

eCRFs will be programmed with real-time validation checks to alert data entry users to missing data, check numeric variables and dates are within ranges and check for consistency across the data.

The first QC review will ensure all applicable questions were completed. During the second QC, copies of the scanned participant’s medical documents will be compared against the eCRF data to ensure data matches. Should problems be identified, data queries will be generated in the REDCap data capture system. Query responses will be reviewed by the delegated study staff and closed once resolved. External data quality audits will be completed by the study Sponsor.

Ethical approval

Ethical approval was sought for the conduct of this study from the Makerere University School of Medicine Research Ethics Committee SOMREC (#2020-089), Uganda National Council of Science and Technology (#HS623S) and St George’s School of Medicine Research Ethics Committee (#2020.0146).

Stakeholder engagement

Extensive stakeholder engagement will occur locally and nationally. Local community representatives and leaders from the ten parishes surrounding KNRH will be invited to attend study sensitisation events. Information will be presented on the study aims, objectives and methodology and their views heard. At the national level, the Ministry of Health, National Drug Authority, local pharmacovigilance experts and organisations active in clinical trials and safety will be invited to a series of events at the beginning, midpoint and end of the study.

Discussion

Monitoring vaccine safety is important at all stages of the vaccine’s development. During a clinical trial, it is important to compare rates of adverse outcomes with background data from the same population from which the vaccine trials participants were selected. Data generated from clinical trials are important for identifying common adverse events following immunisation (AEFI); however, early-phase trials tend to have relatively low numbers of participants, short follow-up and limited diversity in terms of the participants. It is therefore imperative to continue monitoring vaccine safety when the product is more widely used in the general population. Post-licensure surveillance has historically relied on passive surveillance, whereby individuals report potential AEFI to public health government organisations, but these systems are severely limited by under-reporting, especially in LMICs. To better understand the safety profile of maternal vaccines both in late-phase clinical trials and following licensure, surveillance systems need to systematically collect information on vaccines and other medicines taken by pregnant women, pregnancy outcomes, infant health, and the presence of potential confounding factors such as other maternal illnesses and age in addition to the AEFI themselves. Comprehensive AEFI monitoring is vital as delayed recognition can lead to underestimation of AEFI, delayed intervention, harming patients and undermining public confidence in vaccines.

Electronic medical records (EMR) provide an opportunity for utilising improved computer capabilities for AEFI surveillance. Most research in this area has occurred in high-income countries, but recently lower-income settings have introduced EMR in their health facilities. In Uganda EMR are in use across 900 facilities and the Ministry of Health are committed to expansion and scale-up countrywide. This system provides a unique opportunity to test the utility of EMR for detecting and classifying AEFI in a low-income setting. These EMR systems will become increasingly important as the demand for vaccines in these settings grows and certain vaccines such as Ebola and malaria are developed primarily for use in LMICs. The West African Ebola virus epidemic of 2014/15, and ongoing Coronavirus pandemic have further highlighted the need for equitable inclusion of pregnant women in low-resource settings in vaccine research.
The growing recognition of the importance of monitoring drug and vaccine safety in pregnant women, has led to the development of several pregnancy registers in the Africa region. In 2013, a pregnancy exposure registry and birth defects surveillance (PER/BDS) system was initiated in KwaZulu-Natal (KZN), South Africa to assess the impact of antiretroviral treatment (ART) on birth outcomes. A pregnancy exposure registry was subsequently implemented in the two subdistricts in Western Cape Province in 2016. Both sites adapted the World Health Organization (WHO)-recommended approach of prospective data collection on exposures in a cohort of pregnant women from the first antenatal visit until the time of delivery.

Conclusions

This Ugandan pregnancy register will provide detailed and accurate data regarding rates of adverse events in KNRR in preparation for maternal vaccine clinical trials. Development of the EMR system will set the groundwork for post-licensure active surveillance for AEFI in Uganda. Future work must determine how the electronic pregnancy register can be expanded to other healthcare settings in the region and link community records with hospital-based ones in preparation for the implementation of new vaccines given in pregnancy.

Data availability

Underlying data

No data are associated with this article.

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