STUDY PROTOCOL

The safety and immunogenicity of a combined pertussis containing vaccine Tdap for HIV infected pregnant women and their newborns (WoMANPOWER) – A study protocol for a randomized clinical trial [version 1; peer review: awaiting peer review]

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Abstract

Background: Globally there are an estimated 24.1 million cases and 160,700 deaths from pertussis annually in children under five years. The disease burden is higher in low- and middle-income countries, especially the African region, which contributes the largest proportions of cases and deaths. Immunization against pertussis in pregnancy is a recommended strategy for the prevention of infant pertussis in many high-income countries. However, vaccine
immunogenicity and effectiveness may be different in immunocompromised individuals such as women living with HIV. There is a need to generate data on the impact of HIV infection in pregnancy on maternal and infant immunity to vaccines against pertussis.  

**Methods:** This is a phase II, randomized controlled observer blind clinical trial of 100 women living with HIV and 100 uninfected women randomized to either standard vaccines (tetanus diphtheria vaccine, Td) or a tetanus diphtheria-pertussis vaccine (Tdap). Participants aged 18-40 years carrying a low-risk singleton pregnancy with a gestational age between 16 and 26 weeks confirmed on ultrasound scan, with no history of receipt of tetanus or pertussis vaccines in the current pregnancy will be recruited. Women will receive either two doses of Td or a first dose of Td and second dose of Tdap vaccine. Participants will complete 14-day diary cards to monitor reactogenicity. Mother-infant dyads will be followed up until the infant is one year old. The outcomes include: safety for the pregnant woman and infant; anti-pertussis toxin (PT) and anti-filamentous haemagglutinin (FHA) IgG concentrations in maternal, cord and infant blood and breastmilk, compared by maternal HIV status.  

**Discussion:** This study will investigate whether vaccines given to women living with HIV have similar immunogenicity and reactogenicity to vaccines given to pregnant women without HIV and monitor the effect of Tdap in pregnancy on infant immune responses.  

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**Keywords**  
Safety, Immunogenicity, Tdap, HIV, Pregnancy
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Competing interests: Manish Sadarangani has been an investigator on projects funded by GlaxoSmithKline, Merck, Pfizer, Sanofi-Pasteur, Seqirus, Symvivo, Moderna and VBI Vaccines. All funds have been paid to his institute, and he has not received any personal payments. PTH has been an investigator on vaccine research funded by Pfizer, Novavax, Minervax, Moderna, Valneva and Astra Zeneca. All funds have been paid to his institute, and he has not received any personal payments. The other authors declare they have no competing interests.

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Abbreviations

AEs  Adverse Events
ART  Antiretroviral therapy
BC  British Columbia
BCG  Bacille Calmette-Guerin vaccine
CBC  Complete Blood Count
CI  Confidence Interval
COVID-19  Coronavirus disease 2019
CRF  Case Report Form
DAIDS  Division of AIDS
dL  deciliter
DSMB  Data and Safety Monitoring Board
EPI  Expanded Program on Immunization
FHA  Filamentous haemagglutinin
GCP  Good Clinical Practice
GMT  Geometric Mean Titers
HBV  Hepatitis B Virus
HEU  HIV exposed uninfected
HIV  human immunodeficiency virus
ICF  Informed Consent Form
ICMJE  International Committee of Medical Journal Editors
IgG  Immunoglobulin G
IRB  Institutional Review Board
MedDRA  Medical Dictionary for Regulatory Activities
MRC  Medical Research Council
MRC/UVRI  Medical Research Council/Uganda Virus Research Institute
MUII  Makerere University UVRI Centre of Excellence for Infection & Immunity Research and Training
MUIHU  Makerere University Johns Hopkins University Research Collaboration
PCR  Polymerase Chain Reaction
PI  Principal Investigator
PT  Pertussis toxin
QC  Quality check
REC  Research Ethics Committee
SAEs  Serious Adverse Events

SGUL  St George’s University of London
SOMREC  School of Medicine Research and Ethics Committee
Td  Tetanus and diphtheria
Tdap  Tetanus, diphtheria acellular Pertussis
TMG  Trial Management Group
TSC  Trial Steering Committee
TT  Tetanus Toxoid
UN CST  Uganda National Council for Science and Technology
WHO  World Health Organization
wP  whole cell pertussis

Introduction

Pertussis is a respiratory disease caused by Bordetella pertussis and presents as a clinical syndrome with infants having a paroxysmal spasmodic violent cough with a high-pitched “whoop”, and post tussive vomiting. Significant reductions in disease rates were observed after implementation of pertussis vaccines, however there is a resurgence of infant pertussis infections in many countries worldwide. Globally, in children under five years there was an estimated 24.1 million cases and 160,700 deaths from pertussis in 2014. The disease burden is more severe in low- and middle-income countries, especially the African region which contributes the largest proportions of disease burden, with 7.8 million cases and 92,500 deaths occurred in 2014. Infants under one year account for 5.1 million cases and 85,900 estimated deaths in Africa. The highest rates of morbidity and mortality occur in the first three months of life when newborns are mainly reliant on passively transferred IgG antibodies through the placenta for protection.

Both acellular and whole-cell vaccines have been used for the prevention of pertussis, with both vaccines demonstrating high efficacy, although systemic and local adverse events are significantly less common with acellular than with whole-cell vaccines. Maternal immunization with pertussis vaccines has been introduced in some high-income countries that use acellular vaccines in their infant programs. The use of acellular pertussis vaccines in pregnancy in these settings has been shown to be safe and effective at preventing disease. In countries like Uganda where whole cell pertussis vaccines are primarily used in infants there are few studies of maternal tetanus diphtheria acellular pertussis (Tdap) vaccination, which hampers the ability of policy makers to make decisions for their national programs.

The effect of maternal Tdap vaccine on infant immunity from the whole cell pertussis vaccine also needs to be considered, especially in HIV high burden settings like Uganda compared to high income countries where the use of acellular pertussis in pregnancy is routine.

HIV exposed uninfected (HEU) infants have lower antigen-specific antibody concentrations for several vaccines with faster
Vaccination of pregnant women living with HIV may, therefore, need different considerations, including a higher dose of vaccine, a more immunogenic vaccine or more doses with a different schedule so as to increase the level of protection transferred via the placenta to protect the exposed infant\textsuperscript{17,18}.

Vaccine effectiveness and immunogenicity could be affected in immunocompromised individuals, like women living with HIV\textsuperscript{17,20}. The HIV-exposed uninfected infants (HEU) when compared with HIV-unexposed uninfected infants (HUU), tend to have increased morbidity and hospitalization from infectious diseases\textsuperscript{11}. Thus, a better understanding of Tdap vaccine safety, immunogenicity, and infant antibody in the context of maternal HIV infection is important if maternal vaccination is to be fully exploited to protect young infants from this infectious disease\textsuperscript{17,22-24.}

This clinical trial sets out to examine the safety and immunogenicity of Tdap vaccine in the context of maternal HIV infection.

Objectives

General objective:
To determine the safety and immunogenicity of tetanus-diphtheria-acellular pertussis (Tdap) vaccine given in pregnancy to women living with HIV.

Specific objectives:
- To determine the safety profile of Tdap vaccination in women living with human immunodeficiency virus (HIV) in Uganda
- To describe the effect of maternal HIV infection on pertussis-specific immune responses in infants born to women vaccinated with a Tdap in pregnancy
- To determine if Tdap vaccination in pregnancy modifies active immune responses to infants' vaccinations with whole cell pertussis (wP) in the context of maternal HIV infection
- To determine the anti-PT, FHA and tetanus toxoid antibody response in breastmilk from women vaccinated with Td or Tdap in the context of maternal HIV infection.

Study justification

Despite Tdap vaccine being routinely used in high income countries and documented as safe and effective, it is not used in low- and middle- income countries. The findings from this study will inform policy on the incorporation of Tdap vaccination in routine maternal vaccines especially in the low resource setting where both HIV and pertussis prevalence in high and Tdap vaccine is not in use.

Trial design

The WoMANPOWER clinical trial is a Phase II, randomized controlled observer blind trial based at Kawempe National Referral Hospital and Kisenyi Health Centre IV in Kampala, Uganda.

The study population consists of four groups:
1. HIV-uninfected women receiving standard of care vaccines (Td) in pregnancy;
2. HIV-uninfected women receiving Tdap vaccine in pregnancy;
3. HIV-infected women receiving standard of care vaccines (Td) in pregnancy;
4. HIV-infected women receiving Tdap vaccine in pregnancy.

Methods: Participants, interventions and outcomes

Study setting

The study is enrolling pregnant women attending antenatal care at Kawempe National Referral Hospital and Kisenyi Health Centre IV in Kampala Uganda.

Eligibility criteria

Each participant must sign an informed consent form indicating that she understands the purpose of, and procedures required for the study and is willing to participate. In case the participant cannot read or write, the procedures are read out and explained and the informed consent is signed witnessed by a literate third party not involved with the conduct of the study.

All of the following must be present for inclusion:
(i) Participant must be a woman aged 18 years or older, inclusive at day of signing the informed consent form (ICF)
(ii) Pregnant woman at >16 and <26 weeks’ gestation, verified by ultrasound scan at time of first vaccine dose
(iii) Documented HIV test during pregnancy taken by rapid test at the screening visit
(iv) Low risk, singleton pregnancy, as assessed by the study physician based on ultrasound scan and previous obstetric history
(v) The participant is willing to comply with the study procedures, including giving birth at Kawempe National Referral Hospital or Kisenyi Health Centre IV, remaining in the study area until the infant is one year old and is able to provide informed consent for herself and on behalf of the infant

Exclusion criteria:
I. Previous anaphylaxis to any component of Td or Tdap vaccines
II. Vaccination is otherwise contraindicated (per product monographs)
III. Documented to have received four or more previous tetanus toxoid vaccine doses (as this would prevent randomization to Tdap group and receipt of two additional tetanus toxoids containing vaccines)
IV. History of pre-eclampsia or eclampsia in previous pregnancies
V. Gestational diabetes in current pregnancy
VI. Rhesus negative mothers
VII. Multigravida - a mother carrying a fifth pregnancy or more than five pregnancies
VIII. Previous late stillbirth (defined as loss of pregnancy at any time after 28 weeks gestation)
IX. Previous low birth weight baby of less than 2.0 kilograms or premature delivery (defined as a delivery before 37 weeks gestation)
X. Previous neonatal death (defined as death of an infant within the first 28 days of life)
XI. Previous delivery of an infant with a known or suspected genetic or chromosomal abnormality
XII. History of other significant pregnancy related complications judged likely to affect the safety of the mother or infant or to significantly compromise the endpoint data collected
XIII. History of other significant neonatal complications judged likely to affect the safety of the mother or infant or to significantly compromise the endpoint data collected
XIV. Significant maternal chronic illness including but not limited to hypertension requiring treatment, heart disease, lung disease, neurological disorders including a history of epilepsy or recurrent afebrile seizures, kidney disease, liver disease, anemia and other hematological disorders (including sickle cell), endocrine disorders including known diabetes mellitus, autoimmunity
XV. Severe anaemia (hemoglobin less than 7.0g/dL)
XVI. Known syphilis or hepatitis B (HBV) virus positive or found to have syphilis or HBV positive serology during screening
XVII. Any other condition judged to significantly increase the risks to either the mother or the infant within the current pregnancy (including relevant history from previous pregnancies)
XVIII. Receipt of any blood product including human immunoglobulins at any stage during the current pregnancy or plan to receive any blood products during the period or trial participation (receipt of blood products in an emergency or for obstetric reasons will not represent a protocol deviation given such situations are unplanned)
XIX. Clinically suspected or confirmed congenital or acquired clotting or bleeding disorders or the current receipt of medications known to alter clotting or bleeding
XX. Any clinically significant signs or symptoms of acute illness, significant abnormalities in vital signs, an axillary temperature of greater than 38.0°C or any recorded fever (greater than 38.0°C) in the preceding 24 hours.
XXI. Two or more symptoms (nausea/vomiting, diarrhea, headaches, fatigue and myalgia) rated as grade 2 and clinically significant on the maternal systemic reactogenicity scale present at baseline on the day of vaccination.
XXII. Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily
XXIII. Participation in the 4 weeks preceding the trial vaccination or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure
XXIV. History of being treated for pertussis

Who will take informed consent?
If a potential participant is identified, the study team will review the consent process with the participant, including review of the informed consent prior to enrolment. The consent and enrolment process will ensure with high confidence that potential participants understand the potential risks and benefits of vaccination, the study procedures, their right to refuse and/or withdraw from the study at any time point without affecting the health services or care they receive, and without having to disclose a reason for their refusal or withdrawal.

Participants will be required to read the full consent or have a full oral explanation in the presence of an impartial witness in an appropriate language before agreeing to take part in the study. They will be given the opportunity to ask any questions and seek clarification. Written consent will then be obtained by a dated signature or thumbprint.

Additional consent provisions for collection and use of participant data and biological specimens
Separate consent forms are required for consent for use of participant data, biological specimen collection and future use. The consent forms and other study materials can be found as Extended data.

Interventions
Explanation for the choice of comparators
Current evidence indicates reduced immunogenicity of inactivated influenza vaccines in HIV-infected as compared with HIV-uninfected pregnant women and relatively rapid waning of maternal antibodies in HIV-exposed infants (4,12,14). The immunogenicity of tetanus toxoid vaccination (TT) in HIV-infected pregnant women remains largely unexplored. However, a Kenyan study showed that the titers of TT antibodies at delivery were 38% lower in HIV-infected compared with HIV-uninfected women (15), TT is the standard of care in this setting. In light of this, the comparison is women
living with HIV and their infants, compared with their uninfected counterparts and their infants to investigate safety and immunogenicity of Tdap vaccine given during pregnancy.

**Antenatal**: Women in antenatal clinic will have baseline blood tests including a complete blood count (CBC), blood group, syphilis serology, hepatitis B serology and antenatal ultrasound at screening. Women meeting the inclusion criteria are then randomized to receive either standard of care vaccine (Td) or standard of care plus Tdap, four weeks apart.

**Interventional Product**: Td Vaccine (WHO PQ Td Vaccine 0.5M) donated by BioNet Asia. Each dose of the vaccine contains diptheria toxoid (5.0 limits of folocculation (Lf) and tetanus toxoid (5 Lf) adsorbed on aluminium hydroxide. Tdap vaccine (Bssotagen, BioNet Asia) 0.5mL intramuscularly. Each dose of vaccine contains recombinant pertussis toxin (rPT, 5 micrograms), filamentous haemagluttanin (FHA, 5 micrograms) and diphtheria toxoid (2 LF) and tetanus toxoid (7.5 LF) adsorbed on aluminium hydroxide.

**Criteria for discontinuing or modifying allocated interventions**

Consenting to be enrolled in a trial implies agreement with trial treatments, trial follow up and data collection. However, an individual participant may stop treatment early or be stopped early for any one of the following reasons:

- Having received vaccination outside of the study after randomization, but before vaccination by the study team
- The investigator can withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.
- A subject may not be eligible for subsequent vaccination following occurrence of hypersensitivity to any study vaccine or vaccine component.
- Withdrawal of consent by the participant

As participation in the trial is entirely voluntary, the participant may choose to discontinue treatment at any time without penalties or loss of benefits to which they may be entitled. Although not obliged to give a reason for discontinuing their trial treatment/protocol inclusion a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant’s rights. Participants who discontinue protocol treatment, for any of the above reasons, remain in the trial for the purpose of follow up and data analysis.

If a participant chooses to discontinue participation in the trial, they will be offered the option to continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, provided they are willing. However, if the participant confirms they do not wish to participate in the scheduled follow up data collection visits, then data that have already been collected will be kept and analyzed according to the intention to treat analysis for all participants who stop follow up early.

Participants who stop the trial follow up after receiving vaccination will not be replaced. Participants who withdraw prior to vaccination may be replaced.

If there is a change in the national recommendations such that pertussis vaccination in pregnancy is no longer recommended, then the trial management committee will consider if the study should be prematurely stopped. In addition, if the data and safety monitoring board (DSMB) recommends that the study be stopped because of safety concerns, the study will be stopped.

**Strategies to improve adherence to interventions**

During the recruitment of study participants, at least two phone numbers on which the mother can be reached including one for the next of kin will be captured. The health visitors will make telephone calls a week to and a day to each participant’s visit to remind them of their upcoming visit. All efforts will be made to trace a participant who will have failed to report to the clinic by 10am for Vaccination visits and 12pm for other visits on a scheduled visit day. Participants with a history of any missed visit will be scheduled at the earliest possible date of a visit window.

**Relevant concomitant care permitted or prohibited during the trial**

Morbidity will be closely monitored as a safety net for participants, and free access to basic health care will be provided to the mothers and their infants. This includes basic medical treatment for non-severe infections (urinary, respiratory, malaria, skin infections etc.) provided at Kawempe National Referral Hospital clinic during opening hours (open Monday to Thursday 8 a.m. until 4 p.m., and Friday 8 am to 12 pm) and Kisenyi Health Centre IV open Monday to Saturday 8 am to 5 pm. In most cases, if the family incurs costs at referring facilities or out of hours centers, these costs will be reimbursed by the study.

The free health care will be provided to participants until the child is 12 months of age, (including participants subsequently excluded) as well as 24/7 access to study staff via mobile phones.

**Provisions for post-trial care**

All infants will be followed up to ensure they adhere to the Expanded Programme on Immunisation (EPI) vaccines as per routine schedule. The infants born to HIV infected women will have a confirmatory HIV polymerase chain reaction (PCR) at six weeks, nine months and 18 months as per the national routine care. Although infants will be followed up to one year, they will be linked up to the appropriate care for testing at 18 months. All infants will receive routine measles vaccination as per EPI.

Participants will be insured against any harm that results from their participation in this study. Professional indemnity will be provided. This insurance will be purchased from a local insurance provider in line with the Uganda National Guidelines for Research Involving Humans as Research Participants.
Outcomes

Primary outcomes

**Primary Outcome 1:** Anti-pertussis toxin (PT) and anti-FHA IgG concentrations in cord blood or neonatal blood of Tdap-vaccinated HIV-infected vs HIV-uninfected pregnant women.

**Primary Outcome 2:** Anti-pertussis toxin (PT) and anti-FHA IgG concentrations in cord blood or neonatal blood of Tdap-vaccinated vs Td vaccinated pregnant women and whether this differs by maternal HIV status.

**Primary Outcome 3:** Anti-PT and anti-FHA IgG concentrations in infants born to Tdap vaccinated vs Td vaccinated pregnant women 4 weeks after the completion of a series of primary vaccination with 3 doses of wP vaccine, and whether this differs by maternal HIV status.

Secondary outcomes

**Secondary Outcome 1:** Anti-PT and anti-FHA IgG concentrations in HIV-infected and HIV-uninfected pregnant women following Tdap vs Td vaccination during pregnancy (4 weeks post-vaccine & at delivery)

**Secondary Outcome 2:** Anti-PT IgG antibody avidity for all comparisons above

**Secondary Outcome 3:** Serum bactericidal activity for all comparisons above.

**Secondary Outcome 4:** Anti-PT IgG and anti-FHA placental transfer ratios in each of the four groups with comparisons between groups

**Secondary Outcome 5:** Tetanus Toxoid antibody responses in each of the 4 groups with comparisons between groups at all time points including transfer ratio

**Secondary Outcome 6:** Anti-PT, FHA and tetanus antibodies in breastmilk from women vaccinated with Td or Tdap

Participant timeline

Each mother-infant pair will be followed up from study enrolment at >16 weeks gestation until the infant is aged one year.

Antenatal: Women will have baseline blood tests and antenatal ultrasound. Women will then be randomized to standard of care or standard of care plus Tdap. First vaccination will be given up to and including 26 weeks gestation and second vaccine four weeks after first vaccination.

Delivery: maternal and cord blood is drawn at delivery and the infant assessed for external congenital anomalies, if cord blood is missed neonatal infant blood taken within seven days of delivery.

Infants' vaccination: Infants will receive their routine EPI schedule - Bacille Calmette-Guerin (BCG) and oral poliovirus vaccines - at birth, followed by pentavalent tetanus-diphtheria-whole cell pertussis-hepatitis B-Haemophilus influenzae type b and oral poliovirus vaccines at 6, 10 and 14 weeks of age.

Infants' follow up: To assess for any long-term adverse events, mothers will receive a phone call when their babies are 6, 9 and 12 months old to check on the infant’s wellbeing.

A blood sample will be drawn 4 weeks after completion of the primary schedule and 4 weeks after first measles vaccine. A breastmilk sample is taken at each of these visits (see schedule at end of manuscript).

Sample size

To assess non-inferiority of Tdap vaccination between HIV-infected and uninfected women, data published from a study assessing birth antibody concentrations and post primary vaccination concentrations of anti-pertussis IgG in babies born to HIV-infected and HIV-uninfected mothers were used. These data show a standard deviation between concentrations at birth and post primary on a log10 scale of approximately 0.4 and just over a two-fold difference in geometric mean titers (GMTs) (HIV 16.07 vs non-HIV 36.11) at birth and nearly three-fold post primary (HIV 270.1 v Non-HIV 91.7).

With a sample size of 40 in each arm the study would have at least 80% power to demonstrate non-inferiority within a 2-fold margin based on a 2-sided 95% confidence interval (CI) for comparing responses between infants from HIV infected and uninfected mothers or between the vaccinated and unvaccinated arms. Based on previous treatment trials in HIV-infected women at Mulago, we anticipate 15% drop out rate during the study and therefore will recruit 200 women (100 HIV+ and 100 HIV−, 50 per group).

Recruitment

Recruitment of study participants started in October 2020 and the follow up is still ongoing. The main strategies for achieving the required sample include the following:

1. Working with a busy maternity unit like Kawempe National Referral Hospital (KNRH). This provides an opportunity to screen a large number of pregnant women with the aim of teasing out those with low-risk singleton pregnancies.

2. In addition to KNRH, a lower-level health facility within the same catchment area of Kawempe i.e., Kisenyi Health Centre IV will also be used for recruitment of study participants

3. Study staff who are qualified nurse-midwives and Doctors will be involved in the screening and enrolment of participants

4. The local PI is a qualified Obstetrician gynecologist who will be closely working with the team members and a Qualified Pediatrician will be on call as needed.
Assignment of interventions: allocation
Sequence generation
Randomization lists will be developed using STATA 16 (RRID: SCR_012763). The STATA generated randomization lists were uploaded to the REDCap database (RRID:SCR_003445) as a csv file for allocation by the unblinded pharmacy team.

Concealment mechanism
Stratified block randomization using blocks of four (4) with a 1:1 ratio stratified by participant HIV status was used to distribute participants into equal groups (total n=200, 50 per group): standard of care vs standard of care plus Tdap.

Implementation
The allocation sequence will be generated by the study data manager and will be sent to the pharmacy team to prepare the vaccination. Women will be given the vaccine by an unblinded study nurse who has no other role in the study.

Assignment of interventions: blinding
Who will be blinded
Study nursing staff and participants are blinded to the vaccine given and vaccine syringes are covered with an opaque label, obscuring the vaccine. Only the preparing pharmacist is aware of the vaccine used. The vaccine is administered by an unblinded trained nurse who only gives the vaccine and has no other participation in the study. A study nurse who is blinded to the vaccine given observes for immediate reactions to the vaccine in a separate room from where the woman receives her vaccination. The laboratory-based research team conducting the assays will be blinded to subject allocation.

Procedure for unblinding if needed
Full study un-blinding will take place when all data has been entered in the study REDCap database, complete data cleaning and the database locked.

Prior to the end of the study, full un-blinding will only occur after all primary endpoint data as outlined by the study protocol and all clinical endpoints reviewed by the chief investigators, principal investigators and data safety monitoring board (DSMB).

Unplanned or urgent un-blinding will only be undertaken to protect participant safety. This will be in the case of a reported serious adverse event discussed and approved by the study regulatory bodies.

Partial un-blinding only for the principal investigators while the study is still on-going. In the case of acute reaction to the study drug and guided by the trial steering committee and the DSMB. This will be done on a case-by-case basis as approved by study regulatory team.

In the event of a study participant dying during the course of the study, un-blinding will not necessarily occur at that time unless the death was proven to be associated with the study vaccine through adverse events review.

Un-blinding a participant simply to obtain randomization and stratification information will not be accepted. The purpose of the stratification is to maintain balance between the treatment groups.

Procedure
Individual participants will be un-blinded on a case-to-case basis in the event of health emergencies such as severe adverse events. For individual participant un-blinding, the following procedure must be followed:

• There should be completed documentation that contains information on the signs/symptoms, any medical diagnoses that indicates a threat to the life of the participant. This is an exception in emergency situations.

• The study team must complete an un-blinding participant request form. This form will then be forwarded to the DSMB and the steering committee and it will be used to guide the un-blinding process. The form must include the participant study ID, detailed information for the reason behind the un-blinding request.

• Once the request has been discussed and approved, a communication should be sent by email to the study PI. The study PI will then write to the pharmacy team to reveal the vaccine the particular individual received.

• The pharmacy team will reveal the vaccine the particular individual received via an email.

Data collection and management
Plans for assessment and collection of outcomes
Essential data for the study is directly entered into the electronic case report form (eCRF) using the REDCap system, which is stored on a secure Structured Query Language (SQL) server at Makerere University Johns Hopkins (MU-JHU). The database was designed with the help of the MU-JHU data manager and reflects the content of the study e-CRFs. All the scientific data is maintained within a pre-designed database, which is backed up on two external hard drives.

Data are collected on tablets and input directly into REDCap by the clinical staff as each participant is recruited and at each follow up visit. For the laboratory data, data is input into the database by the relevant research assistant/data technician as results become available.

Several steps will be undertaken to ensure the accuracy and reliability of the data collected while conducting this study and these include selection of qualified study staff, review of the protocol and study procedures with all the study personnel before undertaking any study related activities as well as pre study and periodic monitoring visits. Guidelines for the completion of case report forms and handling of samples are provided to study staff, and the accuracy and completeness of the study documents is reviewed by designated quality assurance and control personnel and the study monitor(s). Any discrepancies are resolved by the responsible study staff or as appropriate.
Plans to promote participant retention and complete follow-up
At least three attempts are made reaching out to the mothers at 6 and 9 months using a phone call.

During informed consent process, participants will be informed of the study visits, study procedures, planned retention strategies and all efforts that will be undertaken to contact them in case they miss a visit. Detailed participants’ locator information will be taken on the day of enrolment and participants requested to be escorted home by the study staff to take coordinates and geo mapping of the participant’s home. Locator information will be reviewed at each visit and will be updated whenever participant reports change in location.

Participants will be given transport reimbursement on the scheduled study visits that are out of their routine clinic care visits i.e., visits for blood draws for both mother and baby, as well as and for all the EPI visits. They will also be informed of the free medical consultation and care during the study period. At confirmation of enrolment, the study participants will be issued a visit appointment card with details of the expected visit dates to the clinic. On this card, there is a 24-hour study team phone contact which the participant can reach for help or clarification on any issues.

At each visit the study staff will review the participant’s card and remind them of the date and reason for the next scheduled date.

The health visitors will make telephone calls a week before and a day before each participant’s visit to remind them of their upcoming visit.

The data manager/senior data technician will also generate weekly lists indicating participants expected each week and the respective visit type.

On a daily basis, the study coordinator/nurse coordinator will compile a report indicating those that have turned up and their next appointment dates and also follow up those who failed to attend.

All efforts will be made to trace a participant who failed to report to the clinic by 10am for vaccination visits and 12pm for other visits on a scheduled visit day. Participants with a history of any missed visit, should be scheduled at the earliest possible date of a visit window.

Each health visitor will keep a visit schedule of all participants allocated to her in order to remind them of their visits before the visit date.

Data management
The data management department at the MU-JHU provides guidance on the data quality control systems and tracking systems for patients and laboratory samples. The database adhere to good clinical practice (GCP) as much as possible.

Data and samples will be securely transferred between collaborators using only the unique study ID that will not be linked to patient identifiable information.

Data quality
System queries will be automatically triggered by REDCap (e.g., denoting incomplete data, etc.), built in by the data manager. Review may be required for certain forms or/and fields by the data manager, and manual queries will be done randomly by the nurse coordinator using the hospital file as the source document. Automated legal ranges for some variables, skip patterns and logical checks will be programmed into REDCap to reduce data entry errors by the data manager. Quality check (QC) 1 for any category involved in data collection will be done in real time. This will be done to mainly check for data completeness (no missed fields). QC 1 must be done before the data is uploaded to the server. If a midwife is the one collecting data, then a fellow midwife performs QC 1 on the form and documents in the QC 1 eCRF. Likewise, if the health visitor or nurse or medical officer collects data, a colleague of similar cadre performs QC1. QC 2 will be done for checking logical flow of entered data and the data technician will be responsible for checking this on a daily basis for each participant and each form completed within 24 hours of data entry. This will be done by executing data quality rules within REDCap. The data manager will be responsible for creating the data quality rules that will be executed by the data technician. When study staff correct/update study data in response to data queries, the data manager will review the update data and resolve the query or re-query if given response is unsatisfactory. All opened queries will be closed off within 72 hours / 3 days, an automatic log will be kept within REDCap and will be printed off at the end of each month.

Data sharing
A full data set will be shared on publication on the St George’s Figshare page.

Source documents and access to source data
The study team members will have access to medical records of enrolled participants which serve as source documents. A photocopy of the maternity notes will be made at each visit with the hospital number obscured by a sticker prior to photocopying. These notes are held securely in a locked cabinet on site in a locked office to which only the study coordinator or their delegate has the key. A photocopy of the hospital notes of any medical attendance is arranged and stored in the same way as the maternity notes.

The authorized representatives of the sponsor and the ethics committee may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.
Confidentiality
At enrolment, participants will be allocated a unique identifier. Linkage to the participant will be broken at this point and the individual patients will no longer be identifiable to any of the study team. The exception will be if we identify a woman who has previously undiagnosed syphilis, hepatitis B or HIV infection at point of care screening. If this is the case, the woman will be informed, and her results shared with the clinical team in order to provide the necessary health care and follow up required.

Guarantees of confidentiality and anonymity given to the research participants will be honoured, unless there are clear and overriding reasons (such as criminal offences) to do otherwise. Researchers will practice in accordance with the ‘duty of confidentiality’ and not pass on identifiable data to third parties without participants’ consent.

Data will be stored on a validated online clinical trial database (REDCap). The data management department at MU-JHU will provide guidance on the data quality control systems and tracking systems for patients and laboratory samples. (All lab samples will have a unique identifier). All aspects of the database will adhere to GCP. Data and samples will be securely transferred between collaborators using only the unique study ID that will not be linked to patient identifiable information.

Statistical methods
Stata Version 16 will be used for the analyses.

Primary outcome 1:
Primary analysis: Geometric mean anti-PT IgG concentrations will be calculated for each group with 95% confidence intervals. To assess equivalence, the geometric mean fold ratio with a two-sided 95% CI will be calculated for group 4/group 2 and non-inferiority achieved if the lower end is above 0.50 (the 2-fold equivalence margin).

Additional analysis: To account for differences between HIV positive and negative mothers the ratio of group 4/group 2 will be adjusted in a normal errors’ regression model on logged titers with terms included for covariates including maternal age, gestation and prior vaccination history.

Primary outcome 2:
Primary analysis: Geometric mean anti-PT IgG concentrations will be calculated for each group with 95% confidence intervals. Groups 1 vs 2, 3 v 4 and 1 vs 3 and 2 v 4 will be compared by a t-test or Kruskal-Wallis test if logged data are not normally distributed.

Additional analysis: A normal errors regression model based on logged data will be constructed with terms for vaccine (Td v Tdap) and HIV infected mother (yes/no) and a likelihood ratio test done for the interaction of these terms to see if the vaccine effect is the same in infants born to HIV infected and uninfected mothers. This analysis will include adjustment for covariates including maternal age, gestation and prior vaccination history.

Primary outcome 3:
Primary analysis: Geometric mean anti-PT IgG concentrations will be calculated for each group with 95% confidence intervals. Groups 1 vs 2 and 3 v 4 as well as 1 vs 3 and 2 vs 4 will be compared by a t-test or Kruskal-Wallis test if logged data are not normally distributed.

Additional analysis: A normal errors regression model based on logged data will be constructed with terms for vaccine (Td v Tdap) and HIV infected mother (yes/no) and a likelihood ratio test done for the interaction of these terms to see if the vaccine effect is the same in infants born to HIV infected and uninfected mothers.

This analysis will include adjustment for covariates including maternal age, gestation and prior vaccination history. To further assess whether differences by group are explained by the cord blood concentrations the log (base2) cord blood levels will be added to the model and the significance of the group comparisons reassessed. Groups will then be dropped from the model to estimate the fold effect of a doubling in cord blood concentration on 18-week concentrations. This will be stratified by maternal HIV status if the effect differs by this.

Safety endpoints
The investigators will evaluate the tolerability and safety of the vaccines applied during the study according to their clinical experience and standard procedures at their site. Specific reference will be made to the 2014 WHO/Brighton Collaboration recommended definitions of adverse events (AEs) in pregnancy27. Evaluations will take into account the recorded AEs, clinical laboratory, physical examination, and any other parameter that is relevant for safety assessment. AEs will be fully described and coded according to the Medical Dictionary for Regulatory Activities (MedDRA Dictionary)27. A treatment-emergent analysis of AEs will be done.

Frequency of subjects presenting AEs, AEs leading to withdrawal, adverse drug reactions and serious adverse events (SAEs) will be tabulated for each treatment group by system organ class and preferred term. For laboratory parameters, descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be computed on the actual values and the change from baseline (actual and/or relative) for each parameter. All laboratory values will be categorised according to their normal ranges as below, within or above normal.

A shift table versus baseline will be created. Other safety variables, including e.g., heart rate, need for oxygen therapy, or any significant worsening requiring immediate or intensive medical intervention, will be fully depicted using descriptive statistics. Where relevant, actual values and changes from baseline, and/or shift tables according to normal ranges, will be included. Abnormal findings in physical examinations will be listed. Where proportions are given for adverse events 95% exact confidence intervals will also be calculated.
Secondary endpoint analysis

Secondary outcomes 1, 2, 3, 5 and 6:
This will follow the analyses stated for primary outcome 3 for each time point (additional analysis 2 only applies to the 18-week time point).

Secondary outcome 4:
Logged ratios will be compared between groups using t-tests or Kruskal Wallis test if logged data are not normally distributed.

Interim analyses
No interim analysis is planned.

Methods for additional analyses (e.g., subgroup analyses)
As vaccination of the mother with Tdap will occur between 26- and 36-weeks’ gestation (after standard of care Td dose), we will undertake sensitivity analysis by gestational age to determine any effect of gestational age at receipt of vaccine on antibody concentrations.

Plans to give access to the full protocol, participant level-data and statistical code
Anonymised data will be uploaded to the St George’s open access platform, Figshare at the end of the study once the manuscript is published.

Oversight and monitoring

Composition of the trial steering committee
The trial steering committee (TSC) is composed of two thirds independent members including an independent statistician. The terms of reference, role and responsibilities are found in the supplementary data.

The TSC will be comprised of experts relevant to the area of research. At least 50% of the members of the TSC, including the chair, will be independent of the trial. Non-independent members will also form part of the TSC, including the PIs and other members of the trial management group (TMG). The TSC will meet in person or by conference call prior to the start of recruitment, and at least yearly during the recruitment and follow-up phases of the trial. The secretariat to the TSC is responsible for coordinating the meeting date, time and venue for the TSC meetings.

Primary Functions: The role of the TSC is to provide overall supervision and/ or oversight for the trial on behalf of the Sponsor, St George’s, University of London (SGUL), and MRC, the trial Funder and to ensure that the trial is conducted to accepted standards. The Sponsor, SGUL, is responsible for the overall management of the study. It should be noted that the day-to-day management of the trial is the responsibility of the Principal Investigator.

The main features of the TSC are as follows:
- To provide advice, through its chair, to the PI, SGUL, and MRC on all appropriate aspects of the trial
- To oversee the progress of the trial, adherence to the protocol, patient safety, the consideration of new information of relevance to the trial, dissemination and implementation of results.
- To review the protocol for substantial protocol amendments (in a timely manner) and provide advice to the sponsor and funder regarding approvals of such amendments
- To verify appropriate ethical and other approvals are obtained in line with the project plan
- To provide expert oversight and advice to the investigators on all aspects of the trial

Other specific roles of the TSC are to:
- Maintain confidentiality of all trial information that is not already in the public domain
- Provide advisory recommendations as to the future continuation (or otherwise) of the trial
- Monitor progress of the trial (including recruitment, data collection, compliance, follow-up etc) and encourage the TMG to develop strategies to deal with any problems
- Receive letters of feedback from the DSMB and consider its recommendations
- Assess the impact and relevance of any accumulating external evidence
- Review and advise on any proposals by the TMG concerning any change to the design of the trial, including additional sub-studies
- Oversee the timely reporting of the trial results
- Review and advise on the statistical analysis plan
- Comment on the publication policy
- Comment on the clinical study report
- Comment on any abstracts and presentations of any results during the course of the trial.

Composition of the data safety monitoring committee, its role and reporting structure
An independent data safety monitoring board (DSMB) will be established prior to study start and will be composed of three experts in operational, medical, and biostatistical aspects of clinical trials. All members of the DSMB will be completely uninvolved in the running of the trial and cannot be unfairly influenced by people or institutions involved in the trial. The first DSMB meeting will be convened before the study commences to review the protocol, roles and responsibilities, operating guidelines and monitoring plan. The remit and functions of the DSMB will be described in the DSMB Charter. The DSMB will meet at least annually but more frequently as necessary.
Roles of the DSMB

Stewardship of the trial

The DSMB is responsible for the stewardship of the trial. The stewardship includes continuous review of participant recruitment, accrual, retention, and withdrawal. It further involves oversight of participant management, adherence to protocol-specified regimens, and procedures for data management and quality control. The DSMB will be responsible for safeguarding the interests of trial participants by assessing the safety of the interventions during the trial, and the general progress of the trial.

Specifically, the role of the DSMB will be to:

- Monitor and review participant safety in the trial
- Review participant recruitment, accrual, retention, and withdrawal
- Assess data quality, including completeness (and by so doing encourage collection of high-quality data)
- Evaluate emerging literature which may have an impact on the scientific plausibility or need for the trial

This responsibility will be exercised by providing recommendations about continuing, modifying or stopping the trial. To contribute to enhance the integrity of the trial, the DSMB may also formulate recommendations relating to the selection/recruitment/retention of participants, participant management, improving adherence to protocol-specified regimens, and the procedures for data management and quality control.

The DSMB will be advisory to the TSC and will provide such recommendations to this committee.

Safety monitoring

The DSMB is responsible for safeguarding the interests of trial participants by assessing the safety of the interventions during the trial. The DSMB members have reviewed the protocol prior to the trial start and the plan for the collection of safety data before the first patient is enrolled.

At least one DSMB member is an expert in the potential safety outcomes of the trial.

Adverse event reporting and harms

Methods and timing for assessing and recording safety parameters

All study participants will be observed for at least 30 minutes after a vaccination for evidence of immediate reactions in general and in particular for symptoms of allergic phenomena (such as rashes, itching, or other allergic manifestations). Each study participant will be instructed to complete a diary card for 14 days (where day 1 is day of vaccination) following each administration, to describe local and systemic reactions. The health visitors will visit the participants or call to establish the mother’s health condition, and respond to any concerns that the mother may have and also establish if she is having difficulty completing the diary card.

Adverse events (AEs)

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions. An unexpected adverse event is one that is not listed in the investigator’s brochure or current summary of product characteristics or an event that is by nature more specific or more severe than a listed event.

Methods and timing for assessing adverse events

The period of observation for adverse events extends from the time the study participant receives vaccination until she undergoes the final study examination. Any medical event that occurs after the informed consent form is signed, but prior to being vaccinated and is related to a study procedure, will be documented as an adverse event and recorded on the adverse events CRF. Any medical event that occurs after the informed consent form is signed, but prior to being vaccinated and is not related to a study procedure, will be documented as a pre-existing condition and will be recorded on the medical history CRF. A complete medical history will be noted, and physical examination will be performed on all participant before enrolment. The CRFs will capture the medical history and findings of physical examination done at enrolment to establish a baseline. All adverse events, regardless of severity, will be monitored by the investigator until resolution.

All participants experiencing adverse events - whether considered associated with the use of the study vaccine or not will be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist’s report should be supplied, if possible.

Grading of AEs will be undertaken using the criteria below (based on the 2017 DAIDS table)39

Grade 1 Mild: asymptomatic or mild symptoms; no or minimal interference with usual social & functional activities, intervention not indicated

Grade 2 Moderate: moderate symptoms causing greater than minimal interference with usual social & functional activities, intervention indicated

Grade 3 Severe: severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated

Grade 4 Potentially Life-threatening: symptoms causing inability to perform basic selfcare functions with intervention
indicated to prevent permanent impairment, persistent disability or death

Grade 5: Death

**Serious adverse events (SAEs)**

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

- Death

Adverse events which do not fall into these categories are defined as non-serious.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event (SAE) need not, by definition, be severe.

For our study participants’ hospitalization at less than 37 weeks (gestational age) is classified as an AE related hospitalization. Hospitalizations at >37 weeks for normal labor is not regarded as an AE.

For all AEs, the investigator pursues and obtains information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the School of Medicine Research and Ethics Committee (SOMREC), DSMB, sponsor and Uganda National Council for Science and Technology (UNCST). SAEs shall be reported for the entire duration of the study. Should an investigator be made aware of any SAE occurring any time after the active reporting period, this will be promptly reported.

The PI/designee coordinates the safety monitoring and reporting in the study. SAEs are reported to SOMREC following local law and requirements. SAEs are reported to the DSMB as required as well. A detailed description of DSMB functions and responsibilities and guidelines on the transmission flow of SAEs is provided in the DSMB charter.

Notification of SAE to concerned National Regulatory Authorities follows national law requirements.

All SAEs listed as related to the vaccine will be monitored and these are listed on the WHO website.

**Causality assessment**

The degree of certainty with which an AE/SAE can be attributed to administration of the study vaccines (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of one or more of the following:

- Reaction of similar nature having previously been observed with this vaccine or type of vaccine and/or formulation.
- The event having often been reported in literature for similar types of vaccines

**Frequency and plans for auditing trial conduct**

Monitors participate in all key planned activities, collaborating with implementation of the study. They therefore comply with all the planned monitoring visits.

Audits can from time to time be instituted by the sponsor and these will be undertaken in keeping with requirements of the protocol.

**Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees)**

Protocol amendments are communicated to all relevant parties in real time. No changes to the protocol can occur until all regulatory bodies have approved these. Reconsenting of participants may be required if protocol amendments are made.

**Dissemination plans**

**Research participants and communities.** We will hold meetings with research participants and community leaders both before the start of the work, and to share the results. We will work with community advisory boards to aid public engagement activities.

Our collaborators will be members of our steering group, participating in all aspects of the program and advising on dissemination. We will participate in meetings with policy makers at both district and national level, providing simple practical results digests and briefs for policy-makers and highlighting the extent to which our findings have direct policy implications. We will also link to in-country officers of WHO and correspond directly with WHO head office, when appropriate.

**Wider public in Uganda.** We will utilize open days for schools and undergraduates to communicate to the wider public in Uganda. These were initiated in 2009 at the Uganda Virus Research Institute (UVRI) by our capacity development
program, the Makerere University UVRI Centre of Excellence for Infection & Immunity Research and Training (MUII). Each has hosted about 2000 participants. Open day planning includes consultative meetings with teachers to ensure relevance to students’ needs. Open days facilitate intense engagement with the press. As well, we will exploit other opportunities for engagement with the public and local media. http://www.muii.org.ug/

**Wider global public.** We will engage with the global public through our websites (see above) and through the international media, working with our communications teams to ensure regional and international (as well as local) coverage of significant results. The PI shall liaise with all investigators and strive to consolidate data and results and submit a manuscript for peer-review with a view to publication in a reputable academic journal or similar outlet as the main publication. The PI shall be senior and corresponding author of the main publication. Insofar as compatible with the policies of the publication outlet and good academic practice, the other investigators shall be listed in alphabetic order. Providers of analytical or technical services shall be acknowledged but will only be listed as authors if their services were provided in a non-routine manner as part of a scientific collaboration. Members of the TMG shall only be acknowledged as co-authors as per the International Committee of Medical Journal Editors (ICMJE) guidelines. If there are disagreements about the substance, content, style, conclusions, or author list of the main publication, the PI shall ask the TMG to arbitrate.

**Discussion**

HIV exposed but uninfected infants are at a higher risk of infectious diseases including pertussis (11-13). This is of high concern in countries which report high prevalence of both HIV and pertussis but with no routine maternal vaccination programs against pertussis. In this context, the WoMANPOWER study will provide the data required by policy makers to assist in determining on the role of maternal pertussis immunization in the prevention of infant pertussis. LMIC are also likely to register a significant drop in infant immunization following the coronavirus disease 2019 (COVID-19) pandemic, a major risk for infectious diseases in infants. There has been a significant challenge in timely access to antiretroviral therapy (ART) for HIV infected individuals including pregnant women which may increase the risk of pertussis infection in women living with HIV and their infants.

This data will build on the already existent work undertaken mainly in high income countries which has demonstrated that maternal Tdap vaccination is safe, effective and results in higher pertussis antibody concentrations in infants especially in the first two months of life when they are most susceptible to pertussis infection. Serological data demonstrating the interference with pertussis vaccination in infants following maternal Tdap vaccination have been studied. The additional serological data generated from this study will be specific to maternal Tdap vaccination in context of maternal HIV infection and Infants HIV exposure in utero.

**Trial status**


**Ethics approval and consent to participate**

SOMREC approval: 2020-104; UNCST: HS626ES; NDA approval: CTC0139/2020

Written informed consent to participate will be obtained from all study participants.

**Data availability**

**Underlying data**

No data are associated with this article.

**Extended data**


- This project contains the following extended data: WoMANPOWER Eng AOU for sample storage ICF v 6.0 _17 May 2021.docx
- WoMANPOWER Eng AOU for Scr and Enrol ICF v 6.0 _17 May 2021.doc
- woMANPOWER Eng IS v 6.0_17 May 2021.doc
- WoMANPOWER Eng Main ICF v 6.0 _17 May 2021.doc
- WoMANPOWER Eng Participant ID Card V6.0 - 17 May 21.pub
- WoMANPOWER Eng Sample Storage ICF V6.0 _17 May 2021.doc
- WoMANPOWER Health Visitor Card_V6.0 17 May 21.docx
- WoMANPOWER Lug Sample storage ICF v6.0_17 May 2021.doc
- woMANPOWER Lug AOU for sample storage ICF v 6.0 _17 May 2021.docx
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- WoMANPOWER Lug IS v6.0 _17 May 2021.doc
- WoMANPOWER Lug MAIN study ICF_V 6.0 - 17 May’2021.doc
- WoMANPOWER Lug Participant ID Card V6.0 17 May 21.pub
- WoMANPOWER Participant Diary card_V6.0 17 May 21_English.docx
- WoMANPOWER Participant Diary card_V6.0 17 May 21_Luganda.docx
Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

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Reference Source


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