Safety and immunogenicity of an acellular pertussis vaccine containing genetically detoxified pertussis toxin administered to pregnant women living with and without HIV and their newborns (WoMANPOWER): a randomised controlled trial in Uganda

Eve Nakabembe, Melanie Greenland*, Kyle Amaral*, Bahaa Abu-Raya*, Alexander Amone, Nick Andrews, Liberty Cantrell, Elodie Lesne, Andrew Gorringe, Rachel Halkerston, Nikki Mcstraw, Louisa Dixon, Olivia F Hunter, Paul T Heath, Esther Imede, Mary Kyohere, Philippa Musoke, Annettee Nakimuli, Musa Sekikubo, Stephen Taylor, Valerie Tusubira, Manish Sadarangani†, Kirsty Le Doare†*

Summary

Background Immunisation in pregnancy against pertussis can reduce severe disease in infancy. There are few data on the safety and immunogenicity of vaccines given to pregnant women living with HIV and their infants. We aimed to describe the safety and immunogenicity of a tetanus–diphtheria–acellular pertussis (TdaP) vaccine containing genetically detoxified pertussis toxin given to pregnant women living with HIV and the effect of the vaccine on infant whole-cell pertussis vaccine responses.

Methods We conducted an observer-blind, randomised, phase 2, multicentre, non-inferiority trial evaluating safety and immunogenicity of a vaccine containing genetically detoxified acellular pertussis in pregnant women living with HIV in Uganda. Women aged at least 18 years between 16 weeks and 26 weeks of gestation were randomly assigned to receive the tetanus-diphtheria (Td) vaccine or TdaP vaccine. Stratified block randomisation using blocks of four with a 1:1:1:1 ratio stratified by participant HIV status was used to distribute participants into equal groups (50 participants per group for a total of 200 participants). The intervention was a 0·5 mL single intramuscular dose of TdaP vaccine. Td or TdaP vaccination was randomly assigned to different clinic days using randomisation software. Primary immunogenicity endpoints were anti-pertussis toxin and anti-filamentous haemagglutinin IgG concentrations in infants at delivery and 18 weeks following three doses of a whole-cell pertussis containing vaccine. This study is registered at ClinicalTrials.gov, NCT04589312.

Findings Between Oct 28, 2020, and May 21, 2021, 438 pregnant women were screened and 181 were randomly assigned: 90 to TdaP vaccine (40 HIV-positive participants and 50 HIV-negative participants) and 91 to Td vaccine (41 HIV-positive participants and 50 HIV-negative participants). All participants received Td, and 4 weeks later, 177 received either Td or TdaP. 32 serious adverse events occurred, none related to the study vaccine. At delivery, anti-pertussis toxin IgG concentrations for TdaP versus Td were superior in infants who were HIV-exposed but uninfected (geometric mean ratio 9·61, 95% CI 5·21–17·74) and HIV-unexposed infants (21·6, 11·2–41·7). In infants at 18 weeks, anti-pertussis toxin IgG concentrations for TdaP versus Td-vaccinated mothers were significantly lower for both infants who were HIV-exposed but uninfected (0·19, 0·09–0·43) and infants who were not HIV-exposed (0·17, 0·08–0·33). Serum bactericidal antibody generation following whole-cell pertussis vaccination in infants was not affected.

Interpretation TdaP was safe and immunogenic in pregnant women living with HIV and their infants. TdaP provided superior anti-pertussis toxin IgG concentrations at delivery. Following routine vaccination with whole-cell pertussis vaccine, infants born to women receiving the TdaP vaccine had lower anti-pertussis toxin IgG concentrations than infants born to women receiving Td. In the absence of a correlate of protection against pertussis disease, the clinical significance of this finding is unclear.

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*Contributed equally and are joint first authors

†Contributed equally and are joint senior authors

Department of Obstetrics and Gynaecology, School of Medicine, College of Health Sciences, Makerere University, Kampala, Uganda (E Nakabembe MD, A Nakimuli PhD, M Sekikubo PhD); **Centre for Neonatal and Paediatric Infection and Vaccine Institute, City St George's, University of London, London, UK** (E Nakabembe, P T Heath FRCPCH, M Kyohere MSc, K Le Doare FRCPCH); **Oxford Vaccine Group, NIHR Oxford Biomedical Research Centre, Department of Paediatrics, University of Oxford, Oxford, UK** (M Greenland MSc, L Cantrell MSc); **Department of Paediatrics, University of British Columbia, Vancouver, BC, Canada** (K Amaral MSc, M Sadarangani DPhil); **Vaccine Evaluation Center, BC Children's Hospital Research Institute, Vancouver, BC, Canada** (K Amaral, O F Hunter BA, M Sadarangani); **Makerere University-Johns Hopkins University Research Collaboration, Kampala, Uganda** (A Amone MPH, P Musoke PhD, V Tusubira MSc, K Le Doare, M Kyohere); **UK Health Security Agency, Immunisation and Vaccine Preventable Diseases Department, London, UK** (N Andrews PhD); **UK Health Security Agency, Salisbury, UK** (E Lesne PhD, A Gorringe PhD, R Halkerston PhD,

Introduction

Globally in children younger than 5 years, there are an estimated 24·1 million cases and 160 700 deaths from pertussis annually.[1] The disease burden of pertussis is more severe in low-income and middle-income countries (LMICs), particularly in those in Africa,

N Mcstraw MRes, L Dixon BSc, S Taylor PhD, K Le Doare); **Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene & Tropical Medicine Uganda Research Unit, Entebbe, Uganda** (E Imede MLS); **Departments of Paediatrics, Dalhousie University, Halifax, NS, Canada** (B Abu-Raya PhD)

Correspondence to: Dr Eve Nakabembe, Department of Obstetrics and Gynaecology, School of Medicine, College of Health Sciences, Makerere University, Kampala, Uganda **drevena@yahoo.co.uk**

Research in context

Evidence before this study

We searched MEDLINE and Web of Science for studies on tetanus-diphtheria-acellular pertussis (TdaP) vaccine given to pregnant women living with or without HIV published from database inception to May 27, 2024, with no language restrictions. Our search terms were (Pregnan* [MeSH] OR matern* [MeSH] OR expectan* [MeSH]) AND (HIV OR AIDS) AND (Vaccin* [MeSH] OR immun*[MeSH]) AND (Pertussis OR Whooping cough). We did not find any randomised controlled trials on the TdaP vaccine containing genetically detoxified pertussis toxin administered in the context of HIV. There was only one open-label phase clinical trial study on TdaP vaccine that compared pregnant women living with HIV to those living without HIV; the study however had no control group and did not report on infant responses.

Several studies from high-income countries have shown the protective effect of maternal TdaP vaccines in HIV-negative women. In a study conducted in Thailand, pertussis vaccine formulations containing genetically inactivated pertussis toxin (PTgen) were found to be safe and immunogenic in healthy pregnant Thai women. All studied vaccines containing PTgen were non-inferior to the comparator vaccine containing three purified pertussis antigens: chemically inactivated pertussis toxoid, filamentous haemagglutinin, and pertactin. The only study in low-income and middle-income countries (LMICs), which was done in South Africa and investigated pregnant women living with HIV, was an open-label study using a combined pertussis vaccine containing five purified pertussis antigens: pertussis toxin, filamentous haemagglutinin, pertactin, and fimbriae types 2 and 3. This trial showed a lower fold increase in antibody concentrations at 1 month post-vaccination in pregnant women living with HIV compared with HIV-uninfected women for all pertussis antigens examined in the study. However, this study had no control group and did not report on infant responses. Several studies have shown immunomodulation of HIV-unexposed infant immune responses to both acellular pertussis and whole-cell pertussis vaccines. No studies have investigated immune responses to whole-cell pertussis vaccine among infants who are HIV-exposed but uninfected; this information is important to know because existing evidence shows that HIV-positive individuals and infants who are HIV-exposed but uninfected are at a substantially higher risk of getting severe forms of pertussis than are infants who are not exposed to HIV. The risk of hospitalisation and death from pertussis is greatest in early infancy.

Added value of this study

To our knowledge, this is the first randomised controlled trial to assess the safety and immunogenicity of a combined pertussis vaccine containing genetically detoxified pertussis toxin (TdaP) administered to pregnant women living with HIV and their infants. Our study also describes infant immune responses to whole-cell pertussis in infants who are HIV-exposed but uninfected whose mothers received TdaP vaccine and includes follow-up to 12 months for the mother–baby pair.

Implications of all the available evidence

Taking into consideration the resurgence of pertussis and the growing need for effective low-cost vaccines for vulnerable populations in LMICs and special populations such as pregnant women living with HIV, this vaccine could be an option for policy makers in countries with both a high prevalence of HIV and pertussis to reduce the burden of disease in infancy.

contributing to the largest proportion of cases per annum (7·8 million [33%] and 92 500 [58%] deaths).[1,2]

According to WHO, there are an estimated 1·3 million women living with HIV who become pregnant annually, and this number has remained unchanged in recent years.[3] Pregnant women living with HIV are reported to have poorer immune responses following vaccination during pregnancy than do pregnant women without HIV.[4] Impaired responses could be due to B cell depletion in the pregnant woman or due to reduced placental antibody transfer because of saturation of the Fc receptors, which are responsible for active transport of maternal IgG across the placenta to the fetus in the hypergammaglobuminaemic state of chronic HIV infection.[5]

Infants who are HIV-exposed but uninfected are at an increased risk of vaccine-preventable infectious diseases such as pneumonia and sepsis, with the highest morbidity and mortality occurring during early infancy—a time when maternally acquired antibodies play a crucial role in the protection of the infant.[6] In addition to lower concentrations of placentally transferred antibodies, infants who are HIV-exposed but uninfected could experience faster waning of antibodies, which makes them more vulnerable to infection during this period.[7,8]

In settings with a high burden of HIV, particularly in LMICs, HIV infection has a substantial effect on the burden of pertussis disease. A meta-analysis found that the risk of laboratory-confirmed pertussis in infants living with HIV and in infants who were HIV-exposed but uninfected was 50% and 40% higher, respectively, than in infants who were not exposed to HIV.[9] In addition, the risk of hospitalisation and death from pertussis was higher in infants younger than 1 year than in other age groups.

Immunisation in pregnancy against pertussis using tetanus–diphtheria–acellular pertussis (TdaP) vaccine is routine in many high-income countries and has been proven to be safe and effective to protect against pertussis disease in early infancy. In LMICs, the potential of TdaP immunisation in pregnancy has not been fully explored. Several strategies have been proposed to improve immune responses for pregnant women living with HIV

following vaccination during pregnancy, which include adjustment to the antigen concentrations in the vaccine, use of adjuvanted vaccines, and increasing the number of doses given.[5,10] A better understanding of the TdaP vaccine, and the safety, immunogenicity, and infant responses in the context of maternal HIV infection is therefore required to inform policy decisions.[7,11–13]

In this study, we aimed to describe the safety and immunogenicity of a TdaP vaccine containing genetically detoxified pertussis toxin given to pregnant women living with HIV and the effect of the maternal vaccine on infant whole-cell pertussis vaccine responses.

Methods

Study design

The safety and immunogenicity of an acellular pertussis vaccine containing genetically detoxified pertussis toxin administered to pregnant women living with and without HIV and their newborns (WoMANPOWER) trial was an observer-blind, randomised, phase 2, multicentre, non-inferiority study to determine the safety and immunogenicity of TdaP vaccination in pregnant women living with HIV and pregnant women living without HIV and their infants. Recruitment occurred across two antenatal care health facilities at Kawempe National Referral Hospital and Kisenyi Health centre IV in Kampala, Uganda. Ethics approval to conduct the trial was granted by City St George's, University of London, the School of Medicine Research and Ethics Committee—Makerere University, the Uganda National Council for Science and Technology, and the Uganda National Drug Authority. The CONSORT guideline was followed and the study protocol has been published.[14] The study is registered at ClinicalTrials.gov, NCT04589312.

Participants

The eligibility criteria were pregnant women aged 18 years or older, between 16 weeks and 26 weeks of gestation, with a singleton pregnancy, considered to be at low risk following obstetric ultrasound and on the basis of their medical history and clinical assessment. Participants' HIV status was documented following a rapid test at the screening visit and confirmatory testing at a reference laboratory with CD4 count and viral load. Participants were included if they planned to give birth at one of the two sites, remained in the area until the infant was 12 months old, and provided written informed consent for herself and the infant. The full eligibility criteria have been included in the published protocol.[14]

Randomisation and masking

Participants were individually randomised (1:1:1:1) at enrolment to either standard of care (two doses of Td [tetanus–diphtheria] vaccine)[15] or the intervention (one dose of Td followed by one dose of TdaP) stratified by the mother's HIV status. Clinic days for second vaccinations were randomly allocated to Td or TdaP to ensure masking, minimise protocol deviations, and enable preparation in advance. Randomisation lists were developed in Stata 16 (version RRID:SCR_012763), which were then uploaded to the REDCap database (version RRID:SCR_003445) as a .csv file. Stratified block randomisation using blocks of four with a 1:1 ratio stratified by participant HIV status were used to distribute participants into equal groups (50 participants per group, a total of 200).

Two maternal vaccines were used in the study and were administered by intramuscular injection in the upper arm. The Td vaccine (WHO Prequalified-BioNet-Asia, Prakanong, Bangkok, Thailand) contained diphtheria toxoid (5·0 limits of flocculation [Lf]) and tetanus toxoid (5 Lf) adsorbed on aluminum hydroxide. The TdaP vaccine (Boostagen-BioNet-Asia, Prakanong, Bangkok, Thailand) contained genetically detoxified pertussis toxin (5 µg), filamentous haemagglutinin adhesin (5µg), diphtheria toxoid (2 Lf), and tetanus toxoid (7·5 Lf) adsorbed on aluminum hydroxide. Both were given as 0·5 mL injections.

The pentavalent vaccine used for vaccination of infants was DTPHBHib, supplied by the Serum Institute of India (Pune, India), in which each 0·5 mL dose contained diphtheria toxoid (≤25 Lf, tetanus toxoid ≥2·5 Lf, *Bordetella pertussis* [whole-cell] ≤16 opacity units), recombinant hepatitis B surface antigen (≥10 µg), and purified Haemophilus influenzae type b polysaccharide conjugated to tetanus toxoid (carrier protein; 10 µg) adsorbed on aluminium phosphate (≤1·25 mg).

To maintain blinding for study nursing staff and participants, vaccines were prepared out of sight by a pharmacist and an opaque label was applied to obscure the syringe. The vaccines were administered by a trained nurse who had no other participation in the study. Laboratory staff were blinded to the allocation and statisticians were unblinded throughout the trial.

Procedures

Informed consent was obtained from participants before enrolment. Participants were required to read the consent form or have the consent form read to them in the presence of an impartial witness in their appropriate language (English or Luganda) before consenting. Illiterate participants signed the informed consent with a thumb print witnessed by a literate third party not involved in the conduct of the study. Pregnant women consented for themselves and their unborn infants at enrolment.

All pregnant women received Td as their first vaccination between 16^{+0} weeks and 25^{+6} weeks of gestation and returned for their second vaccination (either Td or TdaP) between 20^{+0} weeks and 29^{+6} weeks of gestation. Women's blood samples for antibodies were collected at enrolment (baseline), 4 weeks following second vaccination, and delivery. Timing deviation of second vaccination for women was defined as vaccination outside of 20^{+0} weeks and 29^{+6} weeks of gestation.

Infant blood samples for antibodies were collected at birth (either cord or neonatal venous blood) and 4 weeks following the third dose of whole-cell pertussis vaccine at the infant 18-week visit. Routine infant vaccines were given at 6 weeks, 10 weeks, 14 weeks, and 9 months old. Timing deviation of infant whole-cell pertussis vaccines was defined as either: outside of 4–8-weeks-old for the first dose, and outside of 8–12-weeks-old for the second dose, and 12–16-weeks-old for the third dose; or the difference between the first and second or second and third vaccinations was less than 4 weeks or greater than 6 weeks. Timing deviation of infant 18-week visit was defined as outside of 16–20-weeks-old, or the difference between the third vaccination to 18-week visit was less than 2 weeks or greater than 6 weeks. There were two infants with a 26-day interval between and six infants with a 27-day interval between the third infant vaccine and 18-week visit.

Participants attended a screening and enrolment visit and those eligible received a first dose of Td vaccine between 16 weeks and 26 weeks of gestation. Participants were randomly assigned at enrolment and returned 4 weeks later to receive their second vaccination of either Td or TdaP between 20^{+0} weeks and 29^{+6} weeks of gestation. Participants completed daily diaries in the 14 days following each maternal vaccination to grade their reactions according to Division of AIDS criteria.[16] For women, outcomes throughout pregnancy, delivery, and up until 12 months post-delivery were collected. Blood samples for antibodies were collected at enrolment (at baseline), 4 weeks following second vaccination, and delivery.

Infants were reviewed at delivery and the outcome recorded. Liveborn infants were followed up until they were 12 months old and received all routine Uganda National Expanded Program on Immunisation schedule vaccines (appendix 1 p 3).[17] Infant blood samples for antibodies were collected at birth (cord or neonatal venous blood) and 4 weeks following the third dose of pentavalent vaccine containing whole-cell pertussis at the 18-week visit.

See Online for appendix 1

Serum and heparin plasma samples were stored at the Medical Research Council laboratory in Uganda and shipped to the Vaccine Evaluation Center in Canada and the Vaccine Immunology laboratory at City St George's, University of London, where antibody analyses were performed. IgG against pertussis toxin and anti-filamentous haemagglutinin were measured by enzyme-linked immunosorbent assays following an in-house, validated protocol.[18] Concentrations were expressed in international units per millilitre (IU/mL). The lower limit of quantification was 2 IU/mL for pertussis toxin and 3·5 IU/mL for anti-filamentous haemagglutinin. An in-house multiplex assay described in appendix 1 (p 35) was used to measure tetanus toxoid-specific serum IgG; the lower limit of quantification was 0·001 IU/mL for anti-tetanus toxoid. Serum bactericidal assays were performed at the UK Health Security Agency laboratories based on the method previously described,[19] and are summarised in appendix 1 (p 34).

Outcomes

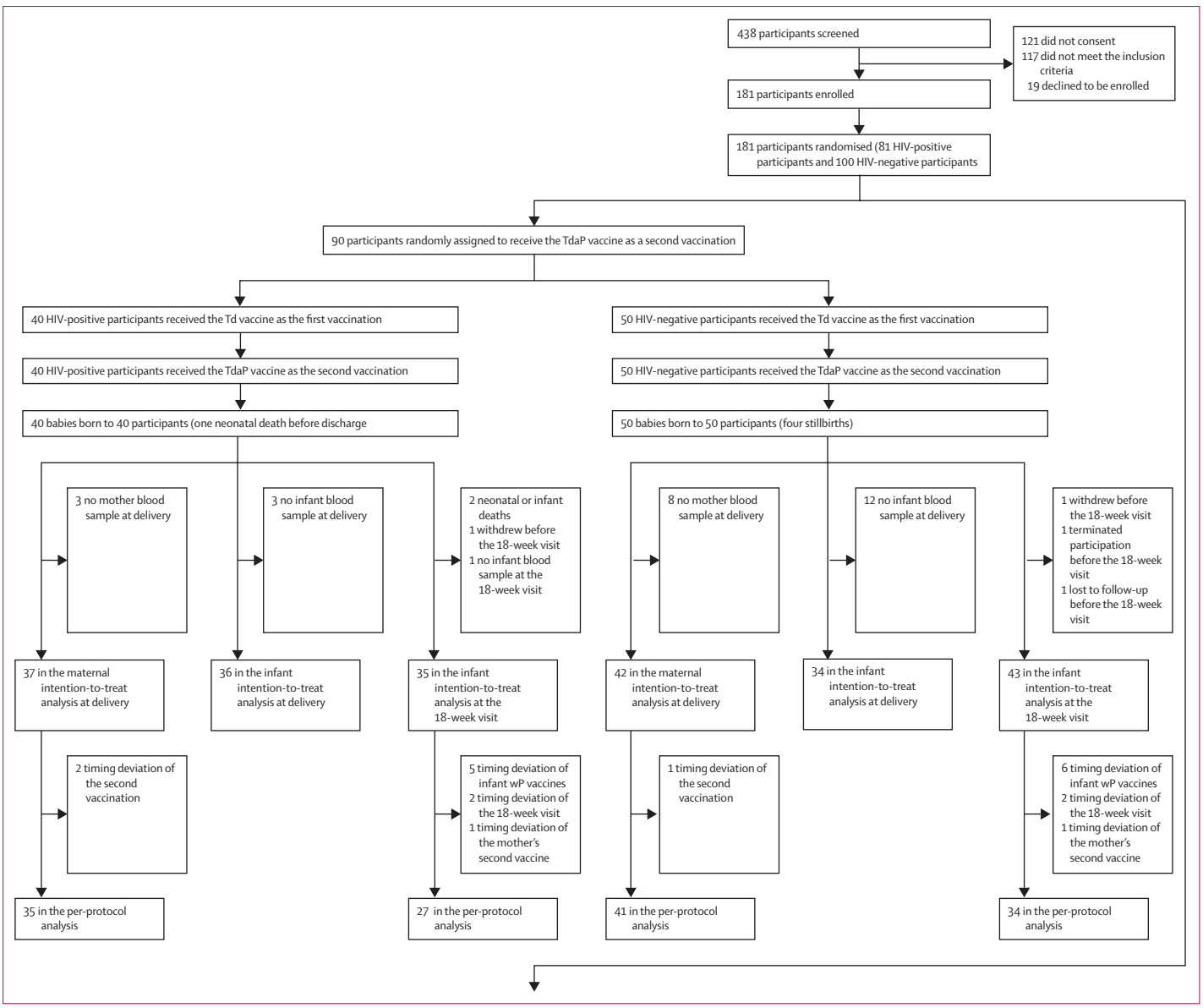
The safety primary outcomes were self-reported solicited local and systemic adverse events in women collected via daily diaries in the 14 days following vaccination, unsolicited adverse events (including medically attended and adverse events leading to withdrawal), and serious adverse events in women and infants throughout the study (appendix 1 p 4). The immunological primary outcomes were anti-pertussis toxin and anti-filamentous haemagglutinin IgG concentrations in the cord or neonatal venous blood, and infant blood 18 weeks following delivery. Secondary outcomes included anti-pertussis toxin and anti-anti-filamentous haemagglutinin IgG concentrations and placental transfer ratios, anti-tetanus toxoid IgG concentrations, and serum bactericidal antibody titres. Other secondary outcomes not described here were anti-pertussis toxin IgG antibody avidity and antibodies in colostrum samples.

Statistical analysis

The safety primary outcomes analyses were conducted on the safety analysis populations and included all women who received a study vaccine and their infants. Frequencies and proportions were calculated for participants with at least one safety event and adverse events reported by group. Each adverse event case was thoroughly reviewed by an independent data safety monitoring board.

The immunogenicity primary outcomes analyses were conducted on the infant modified intention-to-treat populations and excluded those with no blood samples, terminations, withdrawals, or deaths, or incomplete primary infant vaccination series. Immunogenicity outcomes were summarised using geometric mean concentrations (GMCs) and 95% CIs. Geometric mean ratios were calculated as the antilogarithm of the difference between the group means of the $\log_{10}$ transformed titres from a normal errors' linear regression model with $\log_{10}$ titres as the outcome variable and study group as the explanatory variable. The immunogenicity primary outcomes were geometric mean ratios comparing the four study groups: TdaP versus Td within each HIV status group, and HIV-negative versus HIV-positive status of the participant within each of the TdaP and Td groups. Two-sided 95% CIs were used to compare groups.

Individual transplacental ratios were calculated by dividing infant by mother IgG concentrations at delivery and summarised using geometric means. Individual delivery to 18-week fold changes were calculated by dividing infant IgG concentrations at 18 weeks post-delivery by infant concentrations at delivery and summarised using geometric means. Data below the



(Figure 1 continues on next page)

lower limit of quantification were imputed with a value equal to half of the threshold before transformation.

Geometric means of serum bactericidal antibody titres and 95% CIs were calculated for each group for each study timepoint. Kruskal–Wallis tests followed by Dunn's multiple comparisons tests were performed as serum bactericidal antibody titres and were non-normally distributed. Analyses have been reported comparing two timepoints for each study group.

Sensitivity analyses were conducted on the maternal and infant per-protocol populations that further excluded participants who did not receive their trial vaccinations within the schedule timeframes. Sensitivity analyses further adjusting the linear regression models for maternal age at enrolment, gestational age at delivery, and vaccination history (mother received any other vaccines in the past 5 years) were conducted on infant modified intention-to-treat populations at delivery and 18 weeks following delivery. Additional sensitivity analyses were also conducted to further assess differences at 18 weeks following delivery. These linear regression models were adjusted for gestational age at second maternal vaccination, gestational age at delivery, vaccination history, cord or neonatal venous blood concentrations on $\log_2$ scale and intervals between infant vaccinations. Likelihood ratio tests for interaction terms between the study group and maternal HIV status were conducted to determine whether the vaccine effect was

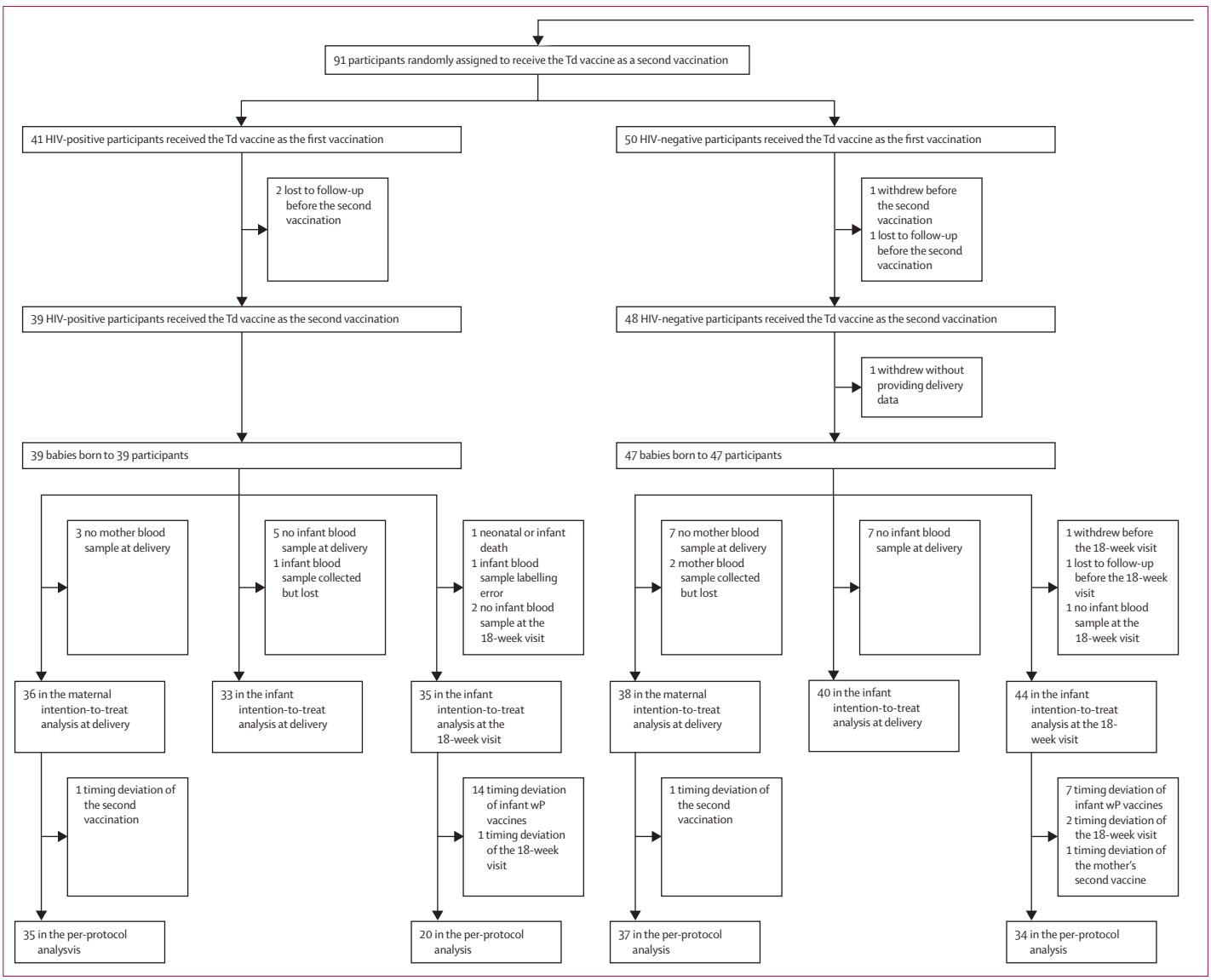


Figure 1: **Trial profile**
TdaP=tetanus-diphtheria-pertussis vaccine. Td=tetanus–diphtheria vaccine. wP=whole-cell pertussis.

the same for infants born to women living with and without HIV.

The trial was designed to detect non-inferiority of the TdaP vaccination between infants who were HIV-exposed and non-exposed at delivery and 18 weeks following delivery after infants received a series of primary vaccinations including three doses of whole-cell pertussis vaccine. The sample size calculation assumed a standard deviation of the immunogenicity primary outcomes to be 0·4 on $\log_{10}$ scale, a non-inferiority margin of 0·5 (0·3 on $\log_{10}$ scale), and the true geometric mean ratio between HIV-positive versus HIV-negative groups or TdaP vaccinated versus Td vaccinated groups to be 1.

The study needed to recruit 50 pregnant women in each group to achieve 90% power at a two-sided 5% significance level, after adjusting for a 15% dropout rate to achieve 40 participants in each study group. However, the sample size was not met and the trial was not sufficiently powered. Formal non-inferiority comparisons were not made but 95% CIs for geometric mean ratios were calculated allowing for informal non-inferiority to be assessed. Statistical analyses were performed using R (version 4.3.1), RStudio (version 2023.12.1+402), SAS (version 9.4), and GraphPad Prism (version 9; GraphPad software, CA, USA).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	HIV-positive TdaP (n=40)	HIV-negative TdaP (n=50)	HIV-positive Td (n=41)	HIV-negative Td (n=50)	Overall (n=181)
Characteristics of the participants					
Age at enrolment (years)					
Mean (SD)	28 (5)	22 (4)	25 (4)	24 (4)	25 (5)
Range	19–41	18–31	19–34	18–34	18–41
Nationality					
Ugandan	39 (97·5%)	50 (100%)	41 (100%)	50 (100%)	180 (99·4%)
Other	1 (2·5%)	0	0	0	1 (0·6%)
BMI at enrolment					
Mean (SD)	26·4 (4·4)	25·1 (4·2)	24·8 (3·3)	24·6 (3·1)	25·2 (3·8)
Range	17·2–38·1	17·7–37·4	19·9–33·6	19·4–31·1	17·2–38·1
Antiretroviral regimen at enrolment					
Option B+ First Line-TDF+3TC+EFV600mg (tenofovir, lamivudine, and efavirenz)	6 (15·0%)	..	6 (14·6%)	..	12 (14·8%)
TDF 3TC DTG (tenofovir with ritonavir, lamivudine, and dolutegravir)	33 (82·5%)	..	35 (85·4%)	..	68 (84·0%)
Other combination ABC with 3TC with DTG (abacavir with ritonavir, lamivudine, and dolutegravir)	1 (2·5%)	..	0	..	1 (1·2%)
CD4 count at enrolment (cells per mL)					
Mean (SD)	621 (299)	..	682 (243)	..	652 (272)
Range	58–1247	..	167–1475	..	58–1475
Viral load: undetectable (<20 copies per mL)	28 (34·6%)	..	23 (28·4%)	..	51 (63%)
Viral load: undetectable (20–1000 copies per mL)	6 (7·4%)	..	8 (9·9%)	..	14 (17·3%)
Viral load: undetectable: unsuppressed (>1000 copies per mL)	6 (7·4%)	..	10 (12·3%)	..	16 (19·7%)
Any previous vaccinations in the last 5 years					
No	36 (90·0%)	48 (96·0%)	40 (97·6%)	45 (90·0%)	169 (93·4%)
Yes	4 (10·0%)	2 (4·0%)	1 (2·4%)	5 (10·0%)	12 (6·6%)
Gestational age at first vaccination (weeks)					
Mean (SD)	20 (2)	21 (2)	21 (3)	21 (2)	21 (2)
Range	16–25	17–24	16–25	16–25	16–25
Gestational age at second vaccination (weeks)*					
Mean (SD)	25 (2)	25 (2)	25 (3)	25 (2)	25 (2)
Range	21–31	21–30	20–30	20–30	20–31
Withdrew or lost to follow-up before second vaccination	0	0	2 (4·9%)	2 (4·0%)	4 (2·2%)
Interval between first and second vaccination (weeks)*					
Mean (SD)	4·6 (0·6)	4·5 (0·6)	4·3 (0·5)	4·6 (0·7)	4·5 (0·6)
Range	4·0–7·0	4·0–6·0	4·0–5·0	4·0–6·0	4·0–7·0
Withdrew or lost to follow-up before second vaccination	0	0	2 (4·9%)	2 (4·0%)	4 (2·2%)
Interval between second vaccination and delivery (weeks)†					
Mean (SD)	14·5 (3·1)	13·3 (4·0)	14·1 (3·1)	13·8 (3·0)	13·9 (3·4)
Range	8·0–20·0	1·0–19·0	8·0–20·0	9·0–20·0	1·0–20·0
Withdrew or lost to follow-up before delivery	0	0	2 (4·9%)	3 (6·0%)	5 (2·8%)
Characteristics of the delivery					
Number of babies	40	50	39	47	176
Gestational age at delivery (weeks)					
Extremely preterm (<28 weeks)	0	2 (4·0%)	0	0	2 (1·1%)
Very preterm (28–32 weeks)	1 (2·5%)	1 (2·0%)	0	0	2 (1·1%)
Moderate to late preterm (32–37 weeks)	1 (2·5%)	1 (2·0%)	0	2 (4·3%)	4 (2·3%)
Term (≥37 weeks)	38 (95·0%)	46 (92·0%)	39 (100%)	45 (95·7%)	168 (95·5%)
Mean (SD)	39 (2)	39 (4)	40 (1)	39 (1)	39 (2)
Range	29–41	24–43	37–44	36–42	24–44
Gestational age at delivery (days)					
Mean (SD)	278 (14)	275 (25)	280 (10)	278 (10)	277 (17)
Range	209–293	169–301	261–310	252–295	169–310

(Table 1 continues on next page)

	HIV-positive TdaP (n=40)	HIV-negative TdaP (n=50)	HIV-positive Td (n=41)	HIV-negative Td (n=50)	Overall (n=181)
(Continued from previous page)					
Preterm (live births before 37 weeks gestation)‡					
Yes	2 (5·0%)	1 (2·2%)	0	2 (4·3%)	5 (2·9%)
No	38 (95·0%)	45 (97·8%)	39 (100%)	45 (95·7%)	167 (97·1%)
Delivery at study site					
Yes	36 (90·0%)	39 (78·0%)	31 (79·5%)	39 (83·0%)	145 (82·4%)
No	4 (10·0%)	11 (22·0%)	8 (20·5%)	8 (17·0%)	31 (17·6%)
Place of delivery (not delivered at study site)					
In a health-centre, clinic, or a different hospital	4 (100%)	9 (81·8%)	4 (50·0%)	6 (75·0%)	23 (74·2%)
At home or another place	0	2 (18·2%)	4 (50·0%)	2 (25·0%)	8 (25·9%)
Mode of delivery					
Spontaneous vaginal	31 (77·5%)	35 (70·0%)	35 (89·7%)	37 (78·7%)	138 (78·4%)
Assisted vaginal-forceps	0	0	1 (2·6%)	0	1 (0·6%)
Planned caesarean section	0	2 (4·0%)	0	0	2 (1·1%)
Vaginal-breech	0	1 (2·0%)	0	0	1 (0·6%)
Emergency caesarean section	9 (22·5%)	12 (24·0%)	3 (7·7%)	10 (21·3%)	34 (19·3%)
Complications during labour					
No	31 (77·5%)	42 (84·0%)	34 (87·2%)	36 (76·6%)	143 (81·3%)
Yes	9 (22·5%)	8 (16·0%)	5 (12·8%)	11 (23·4%)	33 (18·8%)
Infant birth outcomes					
Birth outcome					
Livebirth	40 (100%)	46 (92·0%)	39 (100%)	47 (100%)	172 (97·7%)
Stillbirth	0	4 (8·0%)	0	0	4 (2·3%)
HIV status for infants of HIV-positive women					
HIV-positive	0	..	0	..	0
HIV-negative	37 (92·5%)	..	39 (100%)	..	76 (96·2%)
Unknown	3 (7·5%)	..	0	..	3 (3·8%)
Sex of infant					
Male	19 (47·5%)	20 (40·0%)	19 (48·7%)	25 (53·2%)	83 (47·2%)
Female	21 (52·5%)	29 (58·0%)	20 (51·3%)	22 (46·8%)	92 (52·3%)
Unknown	0	1 (2·0%)	0	0	1 (0·6%)
Birthweight (kg)					
Mean (SD)	3·1 (0·5)	3·1 (0·7)	3·2 (0·4)	3·1 (0·4)	3·1 (0·5)
Range	1·7–4·2	0·9–4·8	2·5–4·5	2·2–4·2	0·9–4·8
Unknown (two stillbirths, one born at home)	0	2 (4·0%)	1 (2·6%)	0	3 (1·7%)
APGAR score at 5 min					
Mean (SD)	10 (1)	9 (2)	10 (1)	10 (1)	10 (1)
Range	4–10	0–10	6–10	7–10	0–10
Unknown (four stillbirths, 27 births not at study site)	4 (10·0%)	12 (24·0%)	8 (20·5%)	7 (14·9%)	31 (17·6%)
Admitted to neonatal intensive care unit					
No	35 (87·5%)	44 (88·0%)	36 (92·3%)	45 (95·7%)	160 (90·9%)
Yes	5 (12·3%)	2 (4·0%)	3 (7·7%)	2 (4·3%)	12 (6·8%)
Unknown (four stillbirths)	0	4 (8·0%)	0	0	4 (2·3%)
Congenital abnormalities					
No	38 (95·0%)	49 (98·0%)	39 (100%)	47 (100%)	173 (98·3%)
Yes	2 (5·0%)	1 (2·0%)	0	0	3 (1·7%)

(Table 1 continues on next page)

Results

From Oct 28, 2020, to May 21, 2021, 438 pregnant women across two study sites in Kampala, Uganda, were screened (figure 1). Of these, 181 (41%) were enrolled and randomly assigned to one of two study groups: 90 (50%) to TdaP vaccine (40 HIV-positive participants and 50 HIV-negative participants) and 91 (50%) to the Td vaccine (41 HIV-positive participants

	HIV-positive TdaP (n=40)	HIV-negative TdaP (n=50)	HIV-positive Td (n=41)	HIV-negative Td (n=50)	Overall (n=181)
(Continued from previous page)					
Infant vaccinations‡					
Age at first wP vaccination (days)§					
Mean (SD)	44 (3)	44 (4)	46 (5)	44 (5)	45 (4)
Range	39–54	40–68	40–70	31–64	31–70
Lost to follow-up or died before visit	1 (2·6%)	1 (2·2%)	0	1 (2·1%)	3 (1·8%)
Interval between first and second wP vaccination (days)§					
Mean (SD)	29 (3)	30 (4)	30 (5)	31 (10)	30 (6)
Range	27–42	27–45	27–51	23–82	23–82
Lost to follow-up or died before second visit	1 (2·6%)	1 (2·2%)	1 (2·6%)	1 (2·1%)	4 (2·3%)
Interval between second and third wP vaccination (days)§					
Mean (SD)	30 (7)	29 (2)	32 (10)	29 (3)	30 (6)
Range	16–56	26–37	19–71	27–39	16–71
Lost to follow-up or died before third visit	2 (5·1%)	2 (4·3%)	1 (2·6%)	1 (2·1%)	6 (3·5%)
Interval between third wP vaccination and 18-week blood sample (days)§					
Mean (SD)	29 (5)	29 (2)	29 (3)	30 (5)	30 (4)
Range	27–53	28–36	26–41	28–54	26–54
Withdrew, lost to follow-up, died before 18-week visit or did not attend 18-week visit	3 (7·7%)	3 (6·5%)	3 (7·7%)	3 (6·4%)	12 (7·0%)

Data are n (%), unless stated otherwise. Gestational age at enrolment was calculated as 280 days minus the difference in days between the expected due date by ultrasound scan and delivery date. Four stillbirths occurred in tetanus-diphtheria-pertussis (TdaP) vaccinated HIV-negative participants; two stillbirths occurred before 28 weeks, one stillbirth between 28 and 32 weeks, and one stillbirth on or after 37 weeks of gestational age. Tests for HIV in infants were only done for infants of HIV-positive participants. Infant sex was unknown for a stillbirth at 24 weeks. Birthweight was unknown for three infants: two stillbirths and one born at home. Appearance, Pulse, Grimace, Activity, and Respirations (APGAR) of the baby at birth score at 5 min was missing for 31 infants: four stillbirths and 27 births not at the study site. Data on admission to neonatal intensive care unit was missing for four stillbirths. Td=tetanus–diphtheria vaccine. wP=whole-cell pertussis. *Excludes participants who were lost to follow-up or withdrew before the second vaccination (n=4). †Excludes participants who were lost to follow-up or withdrew before delivery (n=5). ‡Denominator excludes stillbirths and deaths during hospital admission (n=5). §Excludes infants who were lost to follow-up or died before corresponding visits.

Table 1: **Baseline and clinical characteristics of participants by study group and HIV-infected status in the safety analysis population**

and 50 HIV-negative participants). All 181 pregnant women received their first Td vaccination and 177 received their second vaccination (either Td or TdaP), with one woman withdrawing and three women being lost to follow-up before the second vaccination, and one woman withdrawing after the second vaccination without providing delivery data.

The mean age of enrolled pregnant women was 25 years (range 18–41) and 180 of 181 participants (99%) were Ugandan (table 1). All enrolled pregnant women living with HIV were on combined antiretroviral therapy (cART), with a mean CD4+ T lymphocyte count of 652 cells per µL (range 58–1475); 69 (85·2%) of 81 participants were receiving a dolutegravir-based regimen. The mean gestational age at first vaccination was 21 weeks (range 16–25), at second vaccination was 25 weeks (20–31), and at delivery was 39 weeks (24–44) with five of 172 (3%) livebirths born preterm at less than 37 weeks of gestation (table 1; appendix 1 p 7).

Most women delivered the baby at a study site (145 [82%] of 181 participants), had a spontaneous vaginal delivery (138 [78%] participants), and had no complications during labour (143 [81%] participants). 36 women (20%) delivered by caesarean section. In total, 176 babies were born to 176 women; four (2%) babies were stillborn, 12 (7%) babies were admitted to neonatal intensive care, and three (1·7%) babies had congenital abnormalities (figure 1, table 1). Following delivery and before the 18-week visit, there were four neonatal or infant deaths and four mother–infant pairs withdrew or terminated their participation (figure 1). None of the infants born to women living with HIV were HIV-positive at birth.

The planned sample size of 40 infants in each group at the 18-week visit after accounting for attrition was not met due to the COVID-19 pandemic (TdaP HIV-positive participants [n=36], TdaP HIV-negative participants [n=43], Td HIV-positive participants [n=36], and Td HIV-negative participants [n=44]). Available samples across timepoints for primary endpoints are summarised in appendix 1 (pp 6–7). None of the pregnant women received any other vaccines such as COVID-19 vaccines during pregnancy.

Women self-reported mostly mild to moderate, transient solicited adverse reactions in days 1–14 following the first and second vaccinations (figure 2; appendix 1 pp 2–3). The reactogenicity profiles were similar between TdaP and Td vaccines. There were 295 unsolicited adverse events in 105 women and 375 in 119 infants, of which the majority were mild to moderate (276 [94%] of 295) in women and (363 [97%] of 375) in

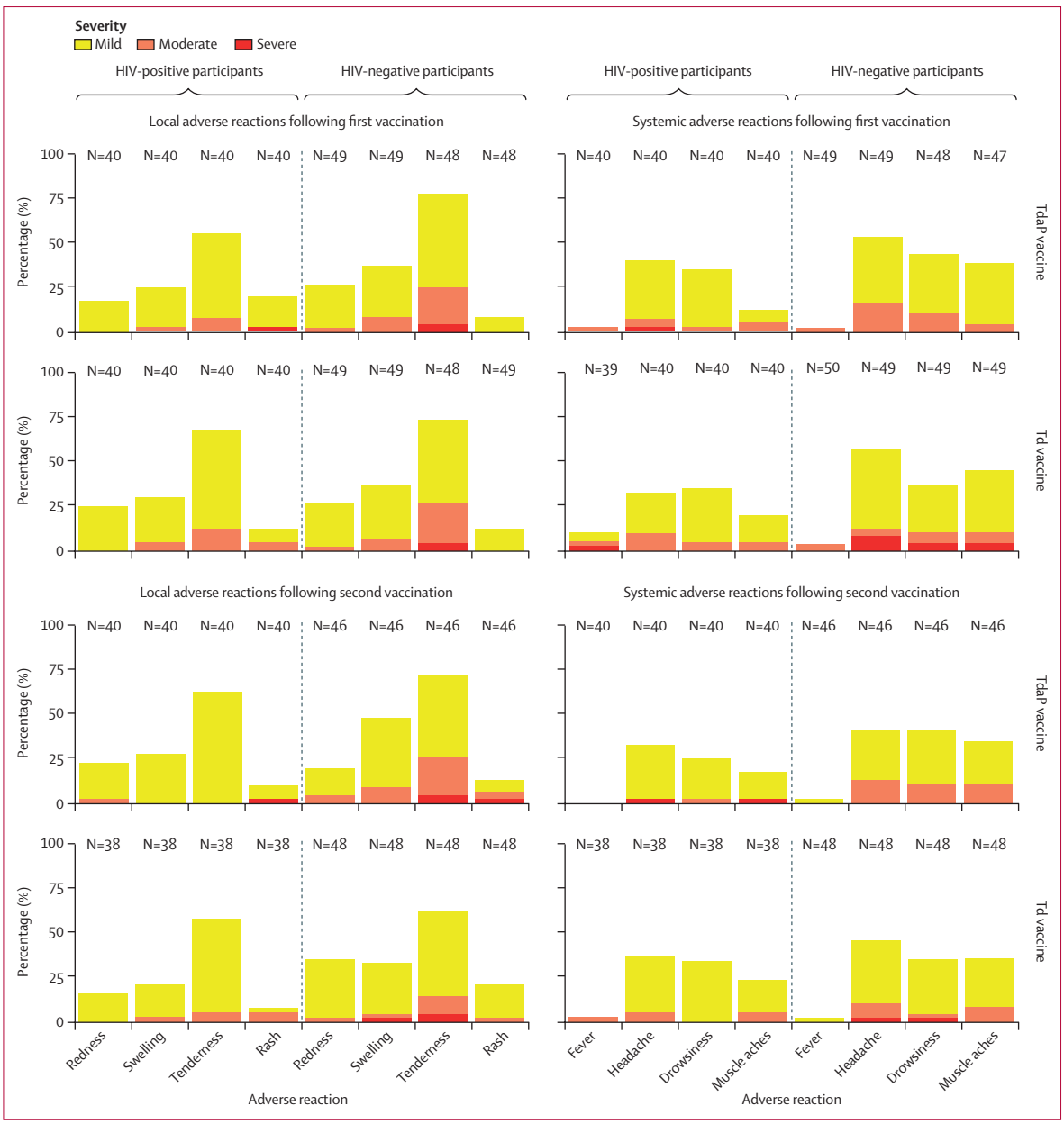


Figure 2: **Reactogenicity—severity of solicited adverse reactions in 14 days after vaccination by study group and HIV-infected status as self-reported in participant diaries in the safety analysis population**

All participants received tetanus–diphtheria (Td) vaccine for their first vaccination. N represents the denominator for each adverse reaction in each study group. The severity presented is the participant's highest severity during 14 days following the vaccination for each solicited adverse event. The participants self-reported local and systemic adverse reactions following vaccination as none, mild, moderate, or severe for headache, drowsiness, muscle aches, redness, swelling, tenderness, and rash. Temperature was collected and fever was defined and graded as no symptoms (<38·0°C), mild symptoms (38·0–38·5°C), moderate symptoms (38·5–39·0°C), severe symptoms (39·0–40·0°C), and potentially life-threatening symptoms (>40·0°C).[20] Data that were either not recorded or poorly recorded were considered missing data. Missing data were excluded in the numerator and denominator and, therefore, denominators do not reflect the participants who were vaccinated but only those with completed reactogenicity data in participant diary cards. TdaP=tetanus-diphtheria-pertussis vaccine. Td=tetanus–diphtheria vaccine.

infants (appendix 1 pp 8–14). Nearly all unsolicited adverse events were medically attended (286 [97%] of 395 in women, 370 [99%] of 375 in infants), and there were no non-fatal unsolicited adverse events that led to study withdrawal. One unsolicited adverse event in the mother was deemed related to the study vaccine (appendix 1 p 14). 24 non-fatal serious adverse events occurred: 15 in women and nine in infants (appendix 1 pp 15–18). There were four intrapartum stillbirths in the TdaP study groups, two early neonatal deaths in the TdaP study groups, and two infant deaths: one in the TdaP group and one in the Td group (appendix 1 pp 19–20). All of the

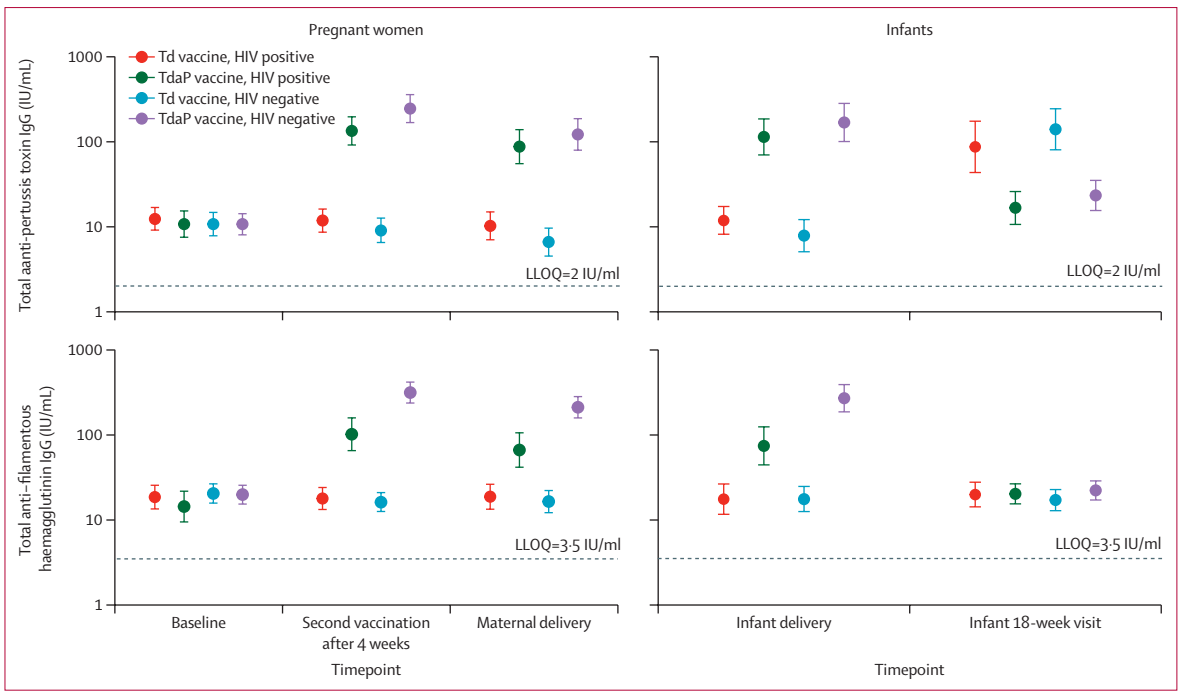


Figure 3: **Kinetics of immunogenicity by study group and HIV status in the modified intention-to-treat populations**
Data presented are geometric mean concentrations and 95% CIs. The boxes indicate the geometric mean concentration and the vertical lines indicate the corresponding 95% CIs. The baseline visit occurred before maternal vaccinations. Infant delivery blood samples were either cord or neonatal venous blood. Infant 18-week visits occurred 4 weeks following the third vaccination dose of whole-cell pertussis in the infant primary vaccination series. TdaP=tetanus-diphtheria-pertussis vaccine. Td=tetanus–diphtheria vaccine. LLOQ=lower limit of quantification.

stillbirths were intrapartum events, resulting from delays in the caesarean section secondary to other co-morbidities. The co-morbidities were obstructed labour (n=2) and severe pre-eclampsia (n=2). One fetus was delivered at 24 weeks and was below the gestational age of viability for Uganda and was considered an abortion using Uganda College of Obstetrics definitions (appendix 1 pp 19–20).

Two (50%) of the four infant deaths occurred several days from time of delivery (96 days and 53 days post-delivery). Both were related to severe pneumonia, which is the most common infectious cause of death in infants younger than 1 year in Uganda (appendix 1 pp 19–20). One death in our study was due to complicated spina bifida, which was not seen on screening ultrasound.

The leading causes of serious adverse events for mothers were severe bladder infections, severe pre-eclampsia, and malaria-complicating pregnancies, which accounted for nine of the 16 events (appendix 1 pp 15–17). Severe pre-eclampsia affecting fetus and newborn sepsis were the most commonly reported infant serious adverse events.

Total anti-pertussis toxin IgG concentrations were similar across the four groups for women at baseline (figures 3, 4; appendix 1 p 21). 4 weeks following the second maternal vaccination, anti-pertussis toxin IgG concentrations for women who received TdaP were more than 11-fold higher than for those who received Td for HIV-positive participants (TdaP GMC 134 [95% CI 91–196], Td GMC 12 [9–16], geometric mean ratio 11·3 [7·0–18·5]) and 27-fold higher compared with Td for HIV-negative participants (TdaP GMC 245 [95% CI 168–358], Td GMC 9 [6–13], geometric mean ratio 27·2 [16·6–44·8]). Similarly, anti-pertussis toxin IgG concentrations at delivery for TdaP versus Td were eight-fold higher for HIV-positive participants (TdaP GMC 87 [95% CI 55–139], Td GMC 10 [7–15], geometric mean ratio 8·54 [4·75–15·38]) and 18-fold higher for HIV-negative participants (TdaP GMC 122 [95% CI 79–187], Td GMC 7 [5–10], geometric mean ratio 18·4 [10·4–32·4]). The same trends were seen at delivery in infants of HIV-positive women (TdaP GMC 115 [95% CI 70–187], Td GMC 12 [8–17], geometric mean ratio 9·61 [5·21–17·74]) and HIV-negative women (TdaP GMC 170 [95% CI 101–285], Td GMC 8 [5–12], geometric mean ratio 21·6 [11·2–41·7]). Conversely, anti-pertussis toxin IgG concentrations at 18 weeks post-delivery following three doses of whole-cell pertussis were higher in infants of Td-recipient women (HIV-positive GMC 88 [95% CI 44–176], HIV-negative GMC 141 [81–246]) compared with infants of TdaP-recipient women (HIV-positive GMC 17 [95% CI 11–26], HIV-negative GMC 23 [16–35]) and were lower in infants of TdaP recipient women compared with Td regardless of HIV status (HIV-positive geometric mean ratio 0·19 [95% CI 0·09–0·43], HIV-negative geometric mean ratio 0·17 [0·08–0·33]).

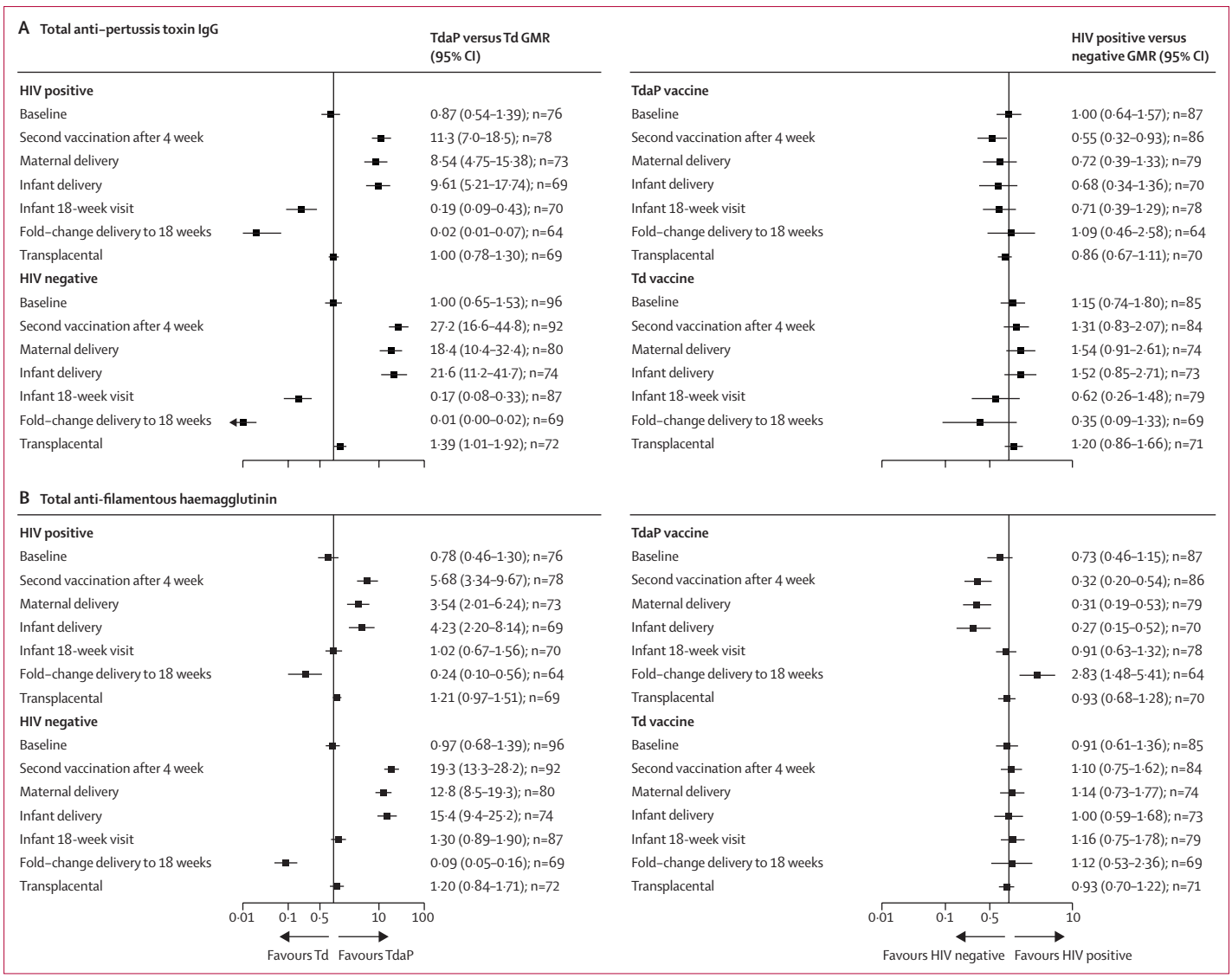


Figure 4: **Immune responses by study group and HIV status in the modified intention-to-treat populations**

Data presented are geometric mean ratios and 95% CIs. The boxes indicate the geometric mean ratio and the horizontal lines indicate the corresponding 95% CIs. The vertical solid line refers to a geometric mean ratio of one and indicates the line of no difference. A CI that lies completely to one side and not intersecting the line of no difference indicates a significant difference in the geometric mean concentrations between the two study groups. GMR=geometric mean ratio. TdaP=tetanus-diphtheria-pertussis vaccine. Td=tetanus–diphtheria vaccine.

Infants of TdaP-recipient women had higher anti-pertussis toxin IgG concentrations than their mothers at delivery (HIV-positive GM of transplacental ratio 1·31 [95% CI 1·17–1·46], HIV-negative GM 1·52 [1·2–1·93]). Transplacental ratios of anti-pertussis toxin IgG concentrations were similar for TdaP versus Td in HIV-positive infant–mother pairs (geometric mean ratio 1·00 [95% CI [0·78–1·30]) but higher for HIV-negative infant–mother pairs (geometric mean ratio 1·39 [1·01–1·92]).

Generally, these trends were similar for anti-anti-filamentous haemagglutinin IgG concentrations in women. However, concentrations in infants following whole-cell pertussis vaccinations at 18 weeks were low regardless of maternal vaccination (figures 3, 4; appendix 1 p 21).

Anti-tetanus toxoid IgG concentrations in infants were similar across the study groups at delivery and at 18 weeks (appendix 1 p 22). The concentrations between delivery and 18-week visit reduced across the study groups. There were no differences between anti-tetanus toxoid IgG concentrations for TdaP versus Td in infants of HIV-positive women or HIV-negative women (appendix 1 23).

At baseline, similar low serum bactericidal antibody titres were observed in maternal samples (table 2). Similar serum bactericidal antibody titres were obtained post-maternal vaccination (4 weeks post-Td or TdaP second-vaccine doses and at delivery), indicating that the

antibodies generated after TdaP vaccination containing anti-filamentous haemagglutinin and genetically detoxified pertussis toxin were not bactericidal against *B pertussis*. Similar serum bactericidal antibody titres were obtained for babies at birth (table 2). An increase in serum bactericidal antibody titres was observed after vaccination of the infants with whole-cell pertussis (18-week-old timepoint). Neither the vaccination status of the mother during pregnancy or HIV status affected this increase. A waning of the serum bactericidal antibody titres was observed for infants aged 10 months of all groups.

HIV-positive TdaP recipients had lower anti-pertussis toxin and anti-anti-filamentous haemagglutinin antibody concentrations than HIV-negative TdaP recipients at 4 weeks following second vaccination (geometric mean ratio 0·55, 95% CI 0·32–0·93; figures 3, 4; appendix 1 p 21). There were no differences between the anti-pertussis toxin antibody concentrations of infants of TdaP recipients who were HIV-exposed but uninfected and infants of TdaP recipients who were not exposed to HIV at delivery (0·68, 0·34–1·36) or at 18 weeks post-delivery (0·71, 0·39–1·29), nor in infants of Td recipients at delivery (1·52, 0·85–2·71) or 18 weeks post-delivery (0·62, 0·26–1·48).

For HIV-positive women versus HIV-negative women who received TdaP, there were significantly lower anti-anti-filamentous haemagglutinin IgG concentrations at delivery (HIV-positive GMC 66 [95% CI 42–106], HIV-negative GMC 211 [158–281]; geometric mean ratio 0·31 [0·19–0·53]). Infants of HIV-positive TdaP-vaccinated women had significantly lower anti-anti-filamentous haemagglutinin IgG concentrations than did infants of HIV-negative TdaP-vaccinated women at delivery (HIV-positive GMC 74 [95% CI 44–124], HIV-negative GMC 270 [186–391]; geometric mean ratio 0·27 [0·15–0·52]). There were no differences in anti-anti-filamentous haemagglutinin antibody concentrations of infants who were HIV-exposed but uninfected versus infants who were not exposed to HIV at 18 weeks for TdaP recipients (geometric mean ratio 0·91, 95% CI 0·63–1·32]), nor for Td recipients at delivery (1·00, 0·59–1·68) or 18 weeks post-delivery (1·16, 0·75–1·78). Anti-anti-filamentous haemagglutinin IgG concentrations waned less in TdaP recipients' infants who were HIV-exposed but uninfected than in infants who were HIV-unexposed (delivery to 18-week fold-change geometric mean ratio 2·83, 95% CI 1·48–5·41]); however, 18 weeks post-delivery concentrations were similar and low across all groups. There were no differences between anti-tetanus toxoid IgG concentrations for infants who were HIV-exposed but uninfected and infants who were not exposed to HIV, for both TdaP and Td recipients' infants (appendix 1 pp 22–23).

There was no significant difference in serum bactericidal antibody titres between women irrespective of vaccination or HIV status (table 2). A slightly higher geometric mean serum bactericidal antibody titre was observed in HIV-negative women at baseline, but similar geometric mean fold changes were obtained for all groups when comparing two study timepoints.

	Td vaccine, HIV-positive	TdaP vaccine, HIV positive	Td vaccine, HIV negative	TdaP vaccine, HIV negative
Mothers				
Baseline (N)	19	19	16	19
Geometric mean	11·8	14·7	13·9	32·9
95% CI	5·3–25·9	7·6–28·1	7·1–27·2	15·3–70·8
4 weeks post-second vaccination (N)	18	19	17	20
Geometric mean	11·2	13·8	14·0	26·6
95% CI	5·6–22·7	7·2–26·7	6·9–28·4	12·9–55·0
Delivery	19	19	18	19
Geometric mean	11·2	17·5	15·9	30·7
95% CI	5·6–22·2	9·0–34·1	9·1–27·8	14·6–64·3
Baseline to 4 weeks post-second vaccination				
Statistical difference	p>0·05	p>0·05	p>0·05	p>0·05
Geometric mean fold change	0·9	0·9	1·0	0·8
Baseline to delivery				
Statistical difference	p>0·05	p>0·05	p>0·05	p>0·05
Geometric mean fold change	0·9	1·2	1·1	0·9
4 weeks post-second vaccination to delivery				
Statistical difference	p>0·05	p>0·05	p>0·05	p>0·05
Geometric mean fold change	1·0	1·3	1·1	1·2
Infants				
Delivery (N)	17	17	17	18
Geometric mean	12·0	13·1	11·9	28·8
95% CI	5·6–25·6	6·6–26·0	5·9–24·1	12·6–65·8
18 weeks (N)	19	15	20	19
Geometric mean	280·1	199·3	383·3	328·7
95% CI	152·9–513·1	132·0–300·8	271·9–540·3	201·1–537·1
10 month (N)	16	13	16	19
Geometric mean	22·1	10·3	27·5	22·1
95% CI	8·8–55·5	5·3–19·9	12·4–61·0	11·1–44·0
Delivery to 18 weeks				
Statistical difference	p<0·0001	p<0·0062	p<0·0001	p<0·0071
Geometric mean fold change	23·3	15·2	32·2	11·4
Delivery to 10 months				
Statistical difference	p>0·05	p>0·05	p>0·05	p>0·05
Geometric mean fold change	1·8	0·8	2·3	0·8
18 weeks to 10 months				
Statistical difference	p<0·0060	p<0·041	p<0·0027	p<0·0001
Geometric mean fold change	0·08	0·05	0·07	0·07

For each time point, geometric means of the serum bactericidal activity (SBA) titres and 95% CIs with N are represented. Distribution of the data was assessed before performing non-parametric Kruskal–Wallis tests followed by Dunn's multiple comparisons tests. No significance difference was observed for each timepoint between groups (not shown). Statistical analysis and geometric mean fold changes between two timepoints for each group have been indicated. SBA titres were assigned as the interpolated serum dilution, which gives 50% of bacterial killing when incubating the bacteria with serial dilutions of mother serum samples at baseline, 4 weeks post-second vaccination with either tetanus–diphtheria vaccine (Td) or tetanus-diphtheria-pertussis vaccine (TdaP) or at delivery and of infant samples at delivery, 18 weeks or 10 months. Six multiple comparisons were performed when testing data obtained from each timepoint (four groups) when 66 multiple comparisons were applied for analysing mother or infant samples (four groups, three timepoints). To simplify the table, the statistical analyses have been reported by comparing two timepoints for each study group.

Table 2: **Serum bactericidal activity of mother and infant serum using B1917 *Bordetella pertussis* strain**

Significant rises in serum bactericidal antibody titres were observed in all infant groups following the whole-cell pertussis vaccination (table 2). Lower serum bactericidal antibody titres were seen in infants born to HIV-positive women at 18 weeks, but this did not reach significance, and their geometric mean fold changes were comparable to those obtained for infants born to HIV-negative women. Those data suggest that the HIV status of the women does not affect the serum bactericidal activity of infant antibody following whole-cell pertussis vaccination; however, the small sample size precludes definitive conclusions.

The conclusions from the sensitivity analyses in the per-protocol populations and in infants at delivery were unchanged from the primary analyses (appendix 1 pp 24–27). Generally, conclusions across the analyses in infant 18-week anti-pertussis toxin and anti-anti-filamentous haemagglutinin concentrations were consistent with the primary analyses (appendix 1 pp 24–27). The effect of vaccine group did not differ by HIV status at the 18-week visit. Study group, gestational age at delivery, and log2 cord or neonatal venous blood concentrations were associated with anti-pertussis toxin concentrations at the 18-week visit (appendix 1 p 28) but not with anti-anti-filamentous haemagglutinin concentrations (appendix 1 p 29).

Discussion

Our study shows the transfer of anti-pertussis toxin and anti-anti-filamentous haemagglutinin IgG to infants who were HIV-exposed but uninfected and infants who were not exposed to HIV following receipt of a pertussis vaccine containing genetically detoxified pertussis toxin given in pregnancy designed for use in LMICs. Our study used a TdaP vaccine containing genetically modified pertussis toxin that has been shown to be superior to TdaP with chemically detoxified pertussis toxin when given to pregnant women in Thailand.[21] Given that this is a low-cost vaccine shown to be effective in women and infants who receive whole-cell pertussis vaccine, there is huge potential to realise the full impact of the vaccine in LMIC settings where maternal Tdap is not routinely given partly due to cost.

Importantly, the TdaP vaccine used in our study has been used commercially in Thailand with an indication for active booster immunisation in individuals 3 years onwards, which includes pregnant women, and its safety has been followed by active pharmacovigilance with no major safety concerns raised.[22,23] Unlike the studies in Thailand, our study was conducted in Africa during the COVID-19 pandemic. We noted five intrapartum stillbirths, all resulting from delays in caesarean section secondary to other co-morbidities. Importantly, each serious adverse event was thoroughly reviewed by our independent data safety monitoring board and not one was deemed to be associated with the vaccine. All stillbirths were deemed avoidable deaths, which are common in LMICs, and were made worse during the COVID-19 pandemic.[24]

Two of the stillbirth cases were in women with severe pre-eclampsia. Pre-eclampsia is the second leading cause of maternal deaths in Uganda at 25% after obstetric haemorrhage (45%).[25,26] Our findings regarding high incidence of pre-eclampsia are similar to the findings from the TdaP study conducted in South Africa,[27] where hypertensive disorders in pregnancy were the most common registered maternal serious adverse event.

One of the issues we highlight is the inability to access timely caesarean sections at the health facilities that worsened during the pandemic. For example, a woman who had moved to the rural area during the COVID-19 pandemic presented to a nearby general hospital with severe obstructed labour and the baby had severe fetal distress but she could not be helped due to inadequate resources. Eventually this mother accessed the caesarean section services from a regional referral hospital when it was too late to save her baby. The delay to get appropriate timely care is one of the documented three delays (delays were at home, in transit, and at health facilities), which account for preventable maternal deaths and newborn deaths in our setting.[26]

In this study, we have shown that, at 18 weeks, anti-pertussis toxin IgG concentrations were higher in infants whose mothers received Td in pregnancy than infants whose mothers received Tdap in pregnancy, irrespective of fetal HIV exposure. This blunting effect has also been well documented in infants from TdaP-vaccinated women who received acellular pertussis vaccines as a primary series, suggesting that blunting is not a result of vaccine type. In a Finnish study in which mothers received TdaP vaccine containing pertussis toxin (8 µg), filamentous haemagglutinin (8 µg), and pertactin (2·5 µg), diphtheria toxin (2·5 Lf) and tetanus toxoid (5 Lf), immunomodulation of anti-pertussis toxin IgG in infants who received hexavalent DTaP-IPV-Hib-Hep B was greatest in infants born to women with the highest anti-pertussis toxin IG concentrations, suggesting an antibody-mediated mechanism for this effect.[28,29] However, the whole-cell pertussis vaccine comprises a greater number of potentially protective components than the acellular pertussis vaccines, which could moderate any reduction in protection caused by blunting of the anti-pertussis toxin IgG response. It was also interesting to note that post whole-cell pertussis antibody function in infants measured by serum bactericidal antibody was not affected by vaccination during pregnancy.

Despite the no known correlates of protection for pertussis disease, it is known that higher concentration of pertussis-specific antibodies—explicitly anti-pertussis toxin and pertactin—are associated with protection from pertussis disease.[21] Therefore, further exploration of the clinical implications of blunting infants' responses to primary vaccination in the context of high maternally derived antibodies is important, particularly in settings

with limited pertussis surveillance like LMICs and those with no routine booster vaccinations.[30]

We have also shown that the acellular pertussis vaccine containing genetically detoxified pertussis toxin and filamentous haemagglutinin was not able to generate bactericidal antibodies following the mother's vaccination during pregnancy, which was expected as it has previously been shown that pertactin (not included in the BioNet-Asia vaccine) is the only acellular pertussis vaccine antigen that generates bactericidal antibodies.[20] Therefore, any bactericidal antibody transferred to the baby via the placenta was not vaccine-induced. The serum bactericidal activity is an important indicator of the function of anti-*B pertussis* antibodies in infants following whole-cell pertussis vaccination. Using this measurement has enabled us to show that the function of the broader antibody response to the whole-cell pertussis vaccine in infants is unaffected by vaccination during pregnancy or HIV status, which is an important finding. This assay is being used to assess pertussis vaccine studies done in Europe and The Gambia (in preparation), and the data from this Ugandan study will add to this dataset. The serum bactericidal antibody is likely to be an important response to pertussis vaccines evidenced by the loss of pertactin expression by disease-causing strains isolated in countries using acellular pertussis vaccines for the longest duration.[20,31]

In our well controlled population, we have shown comparable placental transfer ratios between pregnant women living with HIV and HIV-negative mother–baby pairs, showing active transfer of antibodies across the placenta from women to infants irrespective of the HIV status of the woman. This finding is different to previous studies of vaccines given to pregnant women living with HIV who were not exposed to cART,[32,33] showing the wider benefits of HIV control in maximising placental transfer of antibodies to infants who are HIV-exposed but uninfected.

Our study findings do not differ from those of a recent observational study in Belgium,[34] which investigated the effect of HIV infection on the quality of IgG and memory B cells in pregnant women living with HIV. The Belgium study found that pregnant women living with HIV had reduced pertussis-specific IgG concentrations and Fc-dependent effector functions 1 month post vaccination. HIV infection was also independently associated with decreased concentration of anti-pertussis toxin-specific IgG in cord blood despite the fact that all women included were virally suppressed on ART. Anti-pertussis toxin-specific antibodies transferred less efficiently in pregnant women living with HIV and their infants than in pregnant women without HIV and their HIV-unexposed uninfected infants.

A study of TdaP vaccine use in pregnant women living with HIV from South Africa has shown a lower fold increase in antibody concentrations 1 month post vaccination in pregnant women living with HIV compared with HIV-uninfected women for all pertussis antigens (pertussis toxin, filamentous haemagglutinin, pertactin, and fimbriae) examined in the study.[27] However, unlike our study, the South Africa and Belgium studies used different TdaP vaccine formulations, which contained chemically detoxified pertussis toxin. Even though all of our studies included women on ART, suboptimal maternal immunity and reduced transfer of pertussis-specific antibodies were evident, which could partly explain the increased susceptibility of infants who are HIV-exposed but uninfected to pertussis in Africa.

The strength of this study is the longitudinal follow-up of pregnant women living with HIV and their infants to the age of 12 months following receipt of a genetically detoxified TdaP vaccine. However, we recognise several limitations. Firstly, recruitment challenges due to the COVID-19 pandemic meant the original planned sample size of 50 participants in each group was not met, which limits the reliability of the conclusions, and non-inferiority comparisons were not conducted. However, we had anticipated a 15% attrition rate although our actual rate was only 13%. Secondly, due to the COVID-19 pandemic, we had out-of-window visits, which could have reduced the reliability of our results, although the per-protocol and modified intention-to-treat analyses were reassuringly comparable. Thirdly, 18% of participants did not deliver at a study site due to difficulties inherent to conducting a study in this setting. During the height of the pandemic, we arranged ambulances to transport women to hospital for delivery to mitigate this limitation but could not provide care to women who had moved away from Kampala City. The study population was restricted to pregnancies between 16 weeks and 26 weeks of gestation, limiting the generalisability of the study results to other pregnancy populations but is in line with the current recommendation for TdaP in pregnancy. Furthermore, the trial participants were mostly young Ugandan women, limiting the generalisability of results to other ethnicities and age groups. Finally, low sample numbers in the serum bactericidal antibody analyses limited the comparison between groups.

As new vaccines are introduced into the antenatal immunisation schedule, including for respiratory syncytial virus and combined acellular pertussis (TdaP), there is an essential need to plan ahead for more standardised data on maternal vaccine safety and immunogenicity in special sub-populations such as pregnant women living with HIV. The availability of uniform accurate data and standardised definitions will improve maternal vaccine confidence especially in special sub-populations, such as pregnant women living with HIV, who could require different vaccine formulations or schedules to keep themselves and their infants protected.

Contributors

KLD, MSa, and BA-R conceived the trial. KLD and MSa were joint chief-investigators. KLD, MSa, BA-R, EN, AN, MS, PM, PTH, AG, and NA contributed to the protocol and design of the study. EN led the

implementation of the study. RH, NM, and LD performed the serum bactericidal antibody experiments. EL performed the serum bactericidal antibody experiments and analysis. MG, LC, and EL did the statistical analysis and accessed and verified the underlying data. MG, EN, KA, KLD, and MSa drafted the manuscript. All other authors contributed to the implementation and data collection. All authors reviewed and approved the final report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Equitable partnership declaration

See Online for appendix 2

The authors of this paper have submitted an equitable partnership declaration (appendix 2). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet Global Health*'s broader goal to decolonise global health.

Declaration of interests

KLD has been an investigator on projects funded by Pfizer to their institution. MSa has been an investigator on projects funded by Pfizer, Merck, Moderna, Sanofi-Pasteur, and GSK, and is a chair and deputy chair of two Data Safety Monitoring Boards for COVID-19 vaccine trials involving various vaccines. All funds have been paid to their institute, and MS has not received any personal payments. EN has received clinical research stipend from the Medical Research Council Joint Clinical Trials Round 9 (grant number MR/T004983/1). BA-R is co-investigator on studies funded by GSK, Pfizer, Merck, Moderna, Vaccitech, and Inventprise, has received honoraria for participation in live meetings from Sanofi Pasteur France and Canada related to pertussis and respiratory syncytial virus, and has received nominal payment as a member of the Data Safety Monitoring Board for a study conducted by Chulalongkorn University, Bangkok, Thailand. All funds have been paid to their institute, and BA-R has not received any personal payments. PTH is a member of the Joint Committee on Vaccination and Immunisation and member of the UK National Immunization Technical Advisory Group. OFH was part of a University of British Columbia Summer Student Research Program (from May to July, 2022) and received CA$3200 stipend to conduct research in the Sadarangani laboratory Vancouver, BC, Canada, including, but not limited to, this WoMANPOWER study. PM is a co-investigator on studies funded by City St George's, University of London paid to to their institution. AG has been an investigator on projects funded by the Medical Research Council. ST has been an investigator on research funded by Moderna, UKHSA paid to to their institution, has a funded project to support laboratory tests of pertussis vaccine. All other authors declare no competing interests.

Data sharing

Individual participant data will be made available when the trial is complete, upon requests directed to the corresponding author. After approval of a proposal, data can be shared through a secure online platform.

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