Safety and immunogenicity of a single dose of Tdap compared to Td in pregnant women in Mali and 3 its effect on infant immune responses: a single-centre, randomised, double-blind, active-controlled phase 2 study

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Summary

Background While maternal pertussis vaccination is a strategy to reduce infant morbidity, safety and immunogenicity data are limited in sub-Saharan Africa. We aimed to evaluate the safety of a single dose of tetanus, diphtheria and acellular pertussis vaccine (Tdap) vaccine compared to tetanus and diphtheria vaccine (Td) vaccine in pregnant women in Bamako, Mali and to assess the pertussis toxin (PT) antibody response at birth.

Methods In this phase 2, single-centre, randomised, double-blind, active-controlled study, from 23 January 2019 to 10 July 2019, healthy 18–39 year old women in the second trimester of a singleton pregnancy were randomised 2:1 to receive Tdap or Td. Blood was tested for serum immunoglobulin G (IgG) against PT and other vaccine antigens using a qualified Meso Scale Discovery multiplex immunoassay. The co-primary objectives evaluated safety and birth anti-PT levels. Infant immune responses to whole-cell pertussis vaccine (DTwP) were assessed. Statistical analysis was descriptive. This trial is registered with clinicaltrials.gov, NCT03589768.

Findings 133 women received Tdap and 67 received Td, with 126 and 66 livebirths, respectively. In the Tdap group, 22 serious adverse events (SAEs) including one maternal death occurred in 20 participants (15·0%), with 10 SAEs in 10 participants (14·9%) in the Td group. Among infants, 18 events occurred among 13 participants (10.3%) and 8 SAEs in 6 participants (9.1%), including three and two infant deaths, occurred in Tdap and Td groups, respectively. None were related to study vaccines. Anti-PT geometric mean concentration (GMC) at birth in the Tdap group was higher than in the Td group (55.4 [46.2–66.6] IU/ml vs 7.9 [5.4–11.5] IU/ml). One month after the third dose of DTwP, the GMC in infants born to mothers in the Tdap group were lower compared to the Td group (20.2 [13.7–29.9] IU/ml vs 77.2 [32.2–184.8] IU/ml). By 6 months of age, the anti- PT GMCs were 17.3 [12.8–23.4] IU/ml and 67.1 [35.5–126.7] IU/ml in Tdap and Td groups, respectively. At birth, anti-tetanus toxin (TT) GMCs were higher in infants in the Td vs Tdap group (5.9 [5.0–7.0] IU/ml vs 4.1 [3.5–4.8] IU/ml). Anti-diphtheria toxin GMCs were similar in both groups.

Interpretation Tdap administered to pregnant women in Mali is safe and well-tolerated. Infants of mothers who received Tdap were born with high PT and protective anti-TT antibody levels. By six months of age, after primary vaccination, the PT levels were lower in the Tdap group compared to the Td group. The blunted immune responses to primary DTwP vaccination in the Tdap infant group warrant further study.

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Research in context

Evidence before this study

Maternal pertussis vaccination has been studied in high- and middle-income countries where infant immunisation occurs at an older age and with acellular-pertussis vaccines and is followed by a booster dose. From January 18, 2004 to January 17, 2024, using search terms "maternal pertussis immunization" and "maternal pertussis vaccination" limited to clinical trials, there were 77 unique publications that included 15 articles describing results of vaccine trials of pertussis vaccine in pregnant women where immune responses to pertussis antigens were evaluated. None of these were performed in sub-Saharan Africa and only a study conducted in Thailand evaluated immune responses to primary infant immunization with whole cell pertussis vaccine but at a 2, 4, 6 months schedule.

Added value of this study

Our trial represents the first evaluation of maternal immunization with pertussis-containing vaccine in a setting where early primary infant immunization is with whole-cell pertussis vaccine. Since the major burden of pertussis morbidity and mortality is borne by those living in this type of setting, this evaluation is important and contributes to the knowledge base around the potential benefits of this intervention.

Implications of all the available evidence

Acellular pertussis vaccine administered in the second trimester of pregnancy is a safe and effective way to ensure that neonates are conferred antibody at levels sufficient to protect them in the first months of life, when most pertussis-related deaths occur. Maternal vaccination, followed by infant primary immunization with whole cell pertussis vaccines at 6, 10 and 14 weeks of age results in a blunted infant immune response of unclear significance. Ultimately, the decision on whether to implement a maternal pertussis immunization program must consider the local epidemiology, and the feasibility, effectiveness, and cost. Future studies to assess durability of immune responses, and the potential need for booster doses would provide valuable information.

Introduction

Despite the availability of a vaccine, pertussis burden remains high globally.[1,2] A resurgence in pertussis disease in industrialised countries in recent years has been attributed to a combination of factors, including improved diagnostics, heightened awareness of the disease, a decrease in natural immunity due to low circulation of the pathogen, and decreased duration of protection from acellular pertussis vaccines.[3,4] The highest incidence of serious disease and mortality occurs in infants under two months of age, as they are too young to receive protection through infant pertussis vaccines.[5] Less is known about pertussis in low resource settings. In the Pneumonia Etiology Research for Child Health (PERCH) study, a case–control study of pneumonia aetiology conducted in seven low and middle resource countries (including Mali), pertussis was identified in 2.2% of severe pneumonia hospitalisations and 2.9% of pneumonia deaths and the pertussis case-fatality rate among infants 1–5 months of age at the five African sites was 12.5%. As PERCH excluded children younger than 1 month of age, these are undoubtedly underestimates of pertussis burden.[6]

To address the burden in the youngest infants, many high and middle resource countries have implemented recommendations for pertussis vaccination during pregnancy.[1,5,7] The goal of these recommendations is to achieve protection of young infants through transplacental transfer of maternal antibodies until active immunisation of the infant can occur. In support of this policy, both observational[8,9] and interventional[10,11] studies have shown that antenatal tetanus toxoid, reduced diphtheria toxoid and acellular pertussis adsorbed vaccine (Tdap) given during pregnancy increased infant antibody levels. In the United Kingdom, vaccine effectiveness of maternal immunisation was 91% against laboratory-confirmed clinical pertussis among children younger than three months of age.[12] In the United States, maternal Tdap vaccine given in the third trimester of pregnancy was 77.7% effective against pertussis and pertussis-like illness in infants younger than two months of age and 90.5% effective against hospitalised cases in infants.[13]

Unfortunately, the positive impact of maternal pertussis vaccination cannot be assumed to be generalisable to low resource settings. Maternal antibody transfer in low resource settings may be adversely affected by malnutrition, human immunodeficiency virus infection, malaria, and other factors.[14] In addition, any diminution of primary infant antibody responses by the presence of maternal antibody may be greater in countries that continue to use whole-cell vaccines in the infant primary series.[15,16]

In Mali and many low resource countries, standard of care is to administer to pregnant women at the first prenatal visit a dose of tetanus and diphtheria toxoids adsorbed vaccine (Td). Realising the importance of pertussis prevention in infants too young to receive vaccine, and the lack of data on the impact of maternal vaccination on infant responses in low resource

settings where whole-cell vaccines are used in the infant immunisation schedule, we examined the safety, immunogenicity, and effect on infant anti-pertussis antibody responses of a Tdap vaccine compared to Td vaccine administered during the second trimester of pregnancy to women in Mali. There, the infant vaccination program includes doses of diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTwP) at 6-, 10- and 14-weeks of age and third dose coverage is 77%.[17] Evaluating maternal vaccination with Tdap in this setting will inform maternal immunisation programs.

Methods

Study design and participants

This was a Phase 2, single-centre, randomised, double-blind, active-controlled study. Participants were recruited at a local, public antenatal care clinic in Bamako, Mali, when presenting for routine care. After obtaining informed consent, medical and obstetrical history were reviewed, and a physical examination was performed. Gestational age was established by ultrasound, whenever possible, in combination with date of last menstrual period and fundal height. Eligible women were healthy and aged 18–39 years, pregnant with a singleton foetus with estimated gestational age 14 0/7 through 26 6/7 weeks and willing and able to provide consent. Exclusion criteria included: 1. History of illness that could pose additional risk to the women or the foetus; 2. Infection requiring systemic treatment within seven days prior to study vaccination; 3. History of serious medical event following previous immunisations or history of progressive neurologic disorder; 4. Known or suspected disease that impairs the immune system; 5. History of severe allergic reaction after a previous dose of any vaccine directed against tetanus, diphtheria or pertussis; and 6. High risk for serious obstetrical complication, among others. Acute illness with or without fever was a temporary exclusion criterion. The entire list of eligibility criteria can be found in the Supplementary Material pg 3. While the seroprevalence of Human Immunodeficiency Virus (HIV) infection in our study population is not known, in general, it is reported as 1.1% in Mali.[18]

Ethics

Prior to study implementation, approvals were obtained from the University of Maryland, Baltimore Institutional Review Board, and the Ethics Committee of the Faculté de Medecine de Pharmacie et d'Odonto-stomatologie in Bamako, Mali. The study drug Import Permit was obtained from the Direction de la Pharmacie et du Medicament in Bamako, Mali. Community meetings were held with local leaders at the study site to explain the study and answer questions. Informed consent was obtained from the woman; if she was illiterate, an independent witness was present for the entire process. At the time of delivery, informed consent was confirmed for the participation of her newborn infant.

Randomisation and masking

After obtaining consent, eligibility was confirmed, and the participant was randomised in a 2:1 ratio to receive either Tdap or Td. Additionally, to minimise blood collections, the future infant was assigned in a 1:1 ratio to have specimen collections at one month following the infant's first dose of DTwP at approximately 10 weeks of age, or at one month following the infant's third dose of diphtheria and tetanus toxoids and DTwP at approximately 18 weeks of age. Overall, a simple randomisation scheme of 2:2:1:1 (4 vaccination and follow-up schedule combinations) was implemented using block sizes of 12. The randomization schemes for vaccination assignment and specimen collection schedule were prepared by statisticians at the Data Coordination Centre and accessed online using the enrolment module of Advantage eClinical. A back up randomisation list was stored securely with access limited to unblinded staff and was available if the internet was not accessible.

The unblinded study pharmacist prepared the assigned vaccine in a private, secluded area and it was administered by an unblinded study team member. Though they were in different types of syringes, the two study products were identical in appearance and were administered with the participant turned away. All clinical staff involved in the care of the participant and in assessment of the safety and immunogenicity of the study product were blinded to study assignment.

Procedures

Participants randomised to Tdap received Boostrix (manufactured by GlaxoSmithKline Biologicals) as a single, 0.5 ml intramuscular (IM) dose. Each dose was supplied in a single-dose prefilled syringe and contained 5 flocculation (Lf) of tetanus toxoid (TT), 2.5 Lf of diphtheria toxoid (DT), 8 μg (mcg) of inactivated pertussis toxin (PT), 8 mcg of filamentous hemagglutinin (FHA), and 2.5 mcg of pertactin (PRN, 69 kDa outer membrane protein), aluminium hydroxide as adjuvant, 4.4 mg (mg) of sodium chloride, ≤100 mcg of residual formaldehyde, and ≤100 mcg of polysorbate 80 (Tween 80). Boostrix is not approved by the Mali Regulatory Authority but is prequalified by the World Health Organization (WHO) for persons four years and older. Participants randomised to Td (manufactured by Biological E. Limited) received a single, 0.5 ml IM dose. This is the current standard of care in Mali and the doses used in this study were provided by the Mali Ministry of Health. Each dose of Td has a potency of 2 Lf of DT and 8.8 Lf of TT. The toxoids are adsorbed onto at least 1.5 mg aluminium phosphate. Thimerosal 0.1 mg/ml (ml) is used as a preservative. Td vaccines were provided in 10-dose vials.

After vaccination, participants were observed for 30 min. Subsequent visits occurred at day 4 (at home), day 8 (at home), and day 31 after vaccination, at delivery, and six weeks, 10 or 18 weeks (per the assignment described above), and six months after delivery. The infant was included in all study visits from delivery onward. If delivery occurred prior to the day 31 visit, then the latter visit was not completed (Fig. 1, Supplementary Material pg. 6).

Participants had blood collected at enrolment, 31 days after vaccination, at delivery, and six weeks, ten or 18 weeks, and six months after delivery; breast milk was also collected at delivery and thereafter (Fig. 1, Supplementary Material pg. 6). Their infants provided blood samples at birth (from umbilical cord), at six weeks, 10 or 18 weeks, and six months of age. To ensure that the delivery samples were collected in a timely manner, the study team was present at the site 24 h, seven days a week. If the participant presented to or needed to be transferred to another facility for delivery, then the delivery visit was completed within three days. Infants born to study participants were vaccinated with DTwP through the routine infant immunisation program.

Solicited local and systemic adverse events (AEs), including pain, tenderness, ecchymosis, erythema, induration, feverishness, fatigue, malaise, myalgia, arthralgia, headache, nausea, and allergic reaction were assessed and graded until seven days after vaccination. Ongoing events at the day 8 visit were followed until resolution. Unsolicited AEs were recorded until day 31 and serious adverse events (SAEs) were recorded throughout study participation. Grading scales for specific maternal and infant events are available in the Supplementary Material pg. 9–14. SAEs were adverse events that resulted in death, inpatient hospitalisation or prolongation of hospitalisation, persistent pr significant incapacity, or congenital anomaly/birth defect or were life-threatening or important. The causality of adverse events was determined by the local study investigators.

Laboratory personnel were blinded to the randomisation assignment of all participants. Serum immunoglobulin G (IgG) against antigens: PT, FHA, PRN, fimbriae 2/3 (FIM 2/3), TT, and DT were measured using a qualified Meso Scale Discovery (MSD) multiplex immunoassay that enabled quantitative determination of antibody titres in high throughput format.[19] Briefly, custom plates were printed with commercially available antigens. Assay procedures followed manufacturer's recommendations. A phosphate buffered saline-Tween 20 and non-fat dry milk solution was used as blocking buffer and sample diluent. Bound antibodies were detected with a conjugated SULFO-TAG™ Anti-Human IgG antibody. Electrochemiluminescence (ECL) signals were measured using the MSD QuickPlex SQ 120 reader. An In-House standard (human immune sera) calibrated against the WHO and National Institute for Biological Standards and Control (NIBSC) International Standards for Pertussis (NIBSC 06/140, NIBSC 89/530), Tetanus (NIBSC TE-3), and Diphtheria (NIBSC 10/262) antisera was included in each assay for titre calculation. Curves for each antigen specificity were generated using a four-parameter logistic (4PL) regression, and antibody concentrations of unknown samples were determined by backfitting ECL signals to the In-House standard curves using MSD Discovery Workbench Version 4.0 software. Antibody results were reported as IU/mL.

Study Visit Type	Screening	Enrolment/ Vaccination	Follow-up	Follow-up	Follow-up	Follow-up	Routine Vaccination Visit	Follow-up	Follow-up
Study Visit Number	V00	V01	V04	V05	V06	V07[a]	-	V07[a]	V08
Study Day	-30 to 1	D1	D31±4d	Birth±3d	Birth + 42d±5d	Birth + 70d±5d	Birth + 100d±5d	Birth + 130d±5d	Birth + 180d±7d
EGA or Infant Age[a]	14-26 weeks	14-26 weeks	19-31 weeks	Birth	6 weeks	10 weeks	14 weeks		6 months
	14-26 weeks	14-26 weeks	19-31 weeks	Birth	6 weeks		14 weeks	18 weeks	6 months

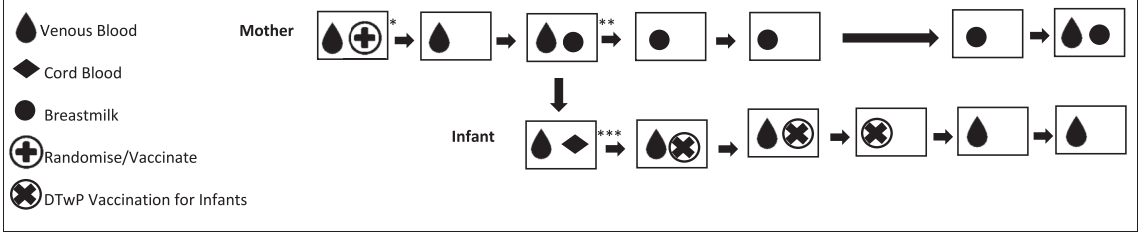

Fig. 1: **Schedule of vaccinations and blood draws for randomised, controlled trial of Tdap vs Td in pregnant women**. Abbreviation: EGA, Estimated Gestational Age. *Prior to study vaccination. **The first colostrum collection may occur within the first 4 days of life of the infant. ***Venous blood from infant within 72 h of birth only if no cord blood obtained. [a]Participants were randomized to have blood sampling at 2.5 months (10 weeks) or 4.5 months (18 weeks) after the birth of the infant.

Outcomes

The co-primary objectives were to evaluate the safety and tolerability, and to assess the PT antibody response at birth, to a single dose of Tdap vaccine compared to Td vaccine in pregnant women. The safety and tolerability of the Tdap in pregnant women was evaluated by measuring the frequency and severity of the following in each vaccine group: 1. study vaccine-related SAEs and all SAEs in pregnant women from study vaccination until 6 months postpartum, 2. AEs specific to pregnancy in pregnant women and their infants, 3. solicited injection site and systemic reactogenicity events from study vaccination until 7 days following vaccination, and 4. all unsolicited non-serious AEs from study vaccination to day 31. The safety of a single maternal Tdap vaccination on the foetus and infant were evaluated by measuring the frequency and severity of AEs specific to pregnancy, in pregnant women and their infants, and study vaccine-related SAEs and SAEs in infants from birth to 6 months of age in each vaccine group. The PT antibody response at birth was assessed by measuring the GMC of serum PT antibody at birth in each vaccine group. Secondary objectives included 1. to assess the antibody response to Tdap vaccine antigens in pregnant women one month after receipt of Tdap or Td, at the time of delivery, and six months after delivery; 2. to compare antibody levels of Tdap antigens at birth (cord blood) and 6 weeks of age (before receiving any infant doses of DTwP) in infants whose mothers received Tdap or Td during pregnancy; 3. to assess placental antibody transfer by determining the ratio of maternal and infant antibody responses at delivery; 4. to assess infant antibody responses to DTwP either prior to the second dose of the primary series, at approximately 10 weeks of age (in half of subjects), at approximately 18 weeks of age (in half of subjects), and at six months of age (all subjects). Additional exploratory objectives are listed in the Supplementary Material (pg. 16) and will not be addressed here.

Statistics

The description of the sample size may be found in the Supplementary Material (pg. 17). Descriptive summary statistics were calculated for serum antibody results for all antigens at relevant timepoints, including the number of subjects with available results and geometric mean concentrations (GMCs) along with 95% confidence intervals (CIs) in each treatment group. The ratio of geometric means (the difference in log values) of the Tdap and Td groups were summarised along with 95% CI where 95% CIs that do not include 1 are considered evidence of a significant difference. All 95% CIs were calculated using the student's t-distribution on log transformed data. Immunogenicity results are reported on the primary immunogenicity populations. The maternal primary immunogenicity population included all pregnant women who received the study vaccination, had valid immunogenicity results from blood at baseline, and at least one post-vaccination visit. The infant primary immunogenicity population included all infants born via live birth to women who received the study vaccination and provided a blood sample for which valid immunogenicity results were reported. Safety data are reported on the safety populations which included all pregnant women who received the study vaccination, and all infants born during the study via live birth to women who received the study vaccination and for whom any data on safety were available.

Role of funding source

National Institutes of Health (NIH) provided regulatory, safety, data, statistical, and monitoring support for the oversight and analysis of the study.

Results

From 23 January 2019 to 10 July 2019, 207 women were screened and 201 were enrolled in the study (Fig. 2), 133 received Tdap and 67 received Td. The median age was 25 years in both groups. In the Tdap group, the median gestational age at enrolment was 18.6 weeks with 44% of women in the 14–17 weeks gestation category. Similarly, in the Td group, the median gestational age at enrolment was 17.6 weeks with 52% in the 14–17 weeks range (Table 1). From 06 May 2019 to 03 January 2020, 192 infants were liveborn and enrolled; 126 (68 males) were born to women in the Tdap group and 66 (34 males) in the Td group. Two women in the Tdap group withdrew from the study and their infants were not enrolled. Median birthweights were similar in both groups. In March 2020, during the follow up period for study participants, SARS-CoV-2 arrived in Mali and field activities were halted. As a result, the visit at 18 weeks of age for the remaining 20 participants were completed over the phone and no blood was collected. Similarly, 173 participants were unable to provide a blood sample at 6 months after delivery/birth (Fig. 2).

Safety outcomes

Table 2 summarises the safety data collected in the study period. In the seven days after vaccination, both vaccines were well-tolerated. Mild pain was the most common symptom, experienced by 7% in the Tdap group and 15% in the Td group. No participant in the Tdap group reported a systemic symptom whereas 4 (6%) participants in the Td group experienced at least a mild one.

Until Day 31 of follow up, in the Tdap group, 29 unsolicited AEs occurred among 26 participants (20%). In the Td group, 15 such events occurred among 11 participants (16%). Twenty-two SAEs involving 20 (15.0%) women were reported in the Tdap group. Of these, one event occurred within 30 days after study vaccination -a spontaneous abortion 26 days after study vaccination. Ten SAEs occurred in 10 (14.9%) women in

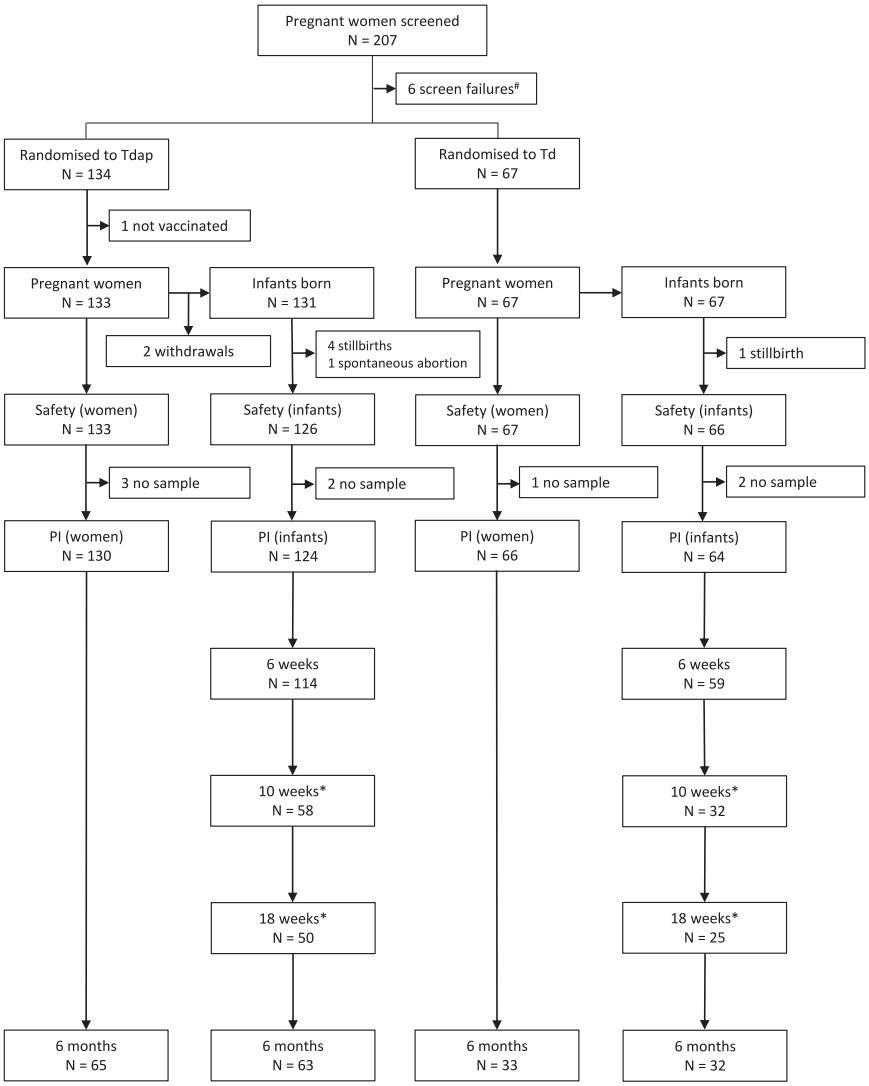

***Fig. 2:* Study profile**. Tdap, tetanus toxoid, reduced diphtheria toxoid and acellular pertussis adsorbed vaccine; Td, tetanus and diphtheria toxoids adsorbed vaccine; PI, Primary immunogenicity analysis includes participants who provided a blood sample at delivery/ birth. # Six screen failures: one multiple gestation, two with known congenital anomalies, one not in good health and one at high risk for a serious obstetrical complication. *Infants were randomised 1:1 to have blood collected at 10 or 18 weeks of age. At 6 weeks timepoint indicates number of participants who provided a blood sample; 124 and 64 participants completed safety follow up in Tdap and Td groups. At 10 weeks timepoint indicates number of participants who provided a blood sample; 62 and 34 participants completed safety follow up in the Tdap and Td groups. At 18 weeks timepoint indicates number of participants who provided a blood sample; 62 and 30 participants completed safety follow up in the Tdap and Td groups. At 6 months timepoint indicates number of participants who provided a blood sample; 130 maternal and 123 infant participants in the Tdap group and 67 maternal and 64 infant participants in the Td group completed safety follow up.

the Td group, none within 30 days of study vaccination. During the follow up period, one maternal death occurred due to eclampsia at 38 weeks gestation in the Tdap group. None of the events were vaccine related.

There were five stillbirths, four and one in the Tdap and Td groups, respectively. Of the stillbirths in the Tdap group, one was due to Rh incompatibility, another due to nuchal cord and 2 were due to unknown cause. The stillbirth in the Td group was due to unknown cause. There was also a spontaneous abortion due to unknown cause that was observed in the Tdap group. Among the infants born in the Tdap group, 38 unsolicited AEs were reported among 23 participants (18%). Among infants born in the Td group, nine unsolicited AEs were reported among seven participants (11%). Among the infants, 18 SAEs were reported in 13 infants (10.3%) in the Tdap group, and eight SAEs were reported in six infants (9.1%) in the Td group. Five infant

	Tdap	Td
Maternal participants (No.)	**133**	**67**
Age (years) [IQR[a]]	25.0 (9.0)	25.0 (8.0)
Age [No. (%)]		
18–29 years old	98 (74)	52 (78)
30–39 years old	35 (26)	15 (22)
Gestational age at vaccination (weeks) [IQR]	18.6 (6.7)	17.6 (7.4)
Gestational age at vaccination [No. (%)]		
14–17 weeks	58 (44)	35 (52)
18–21 weeks	42 (32)	12 (18)
22–26 weeks	33 (25)	20 (30)
Infant participants (No.)	**126**	**66**
Male [No. (%)]	68 (54)	34 (52)
Gestational age at delivery (days) [IQR]	278 (13)	276 (19)
Birth weight (kg) [IQR]	3.20 (0.63)	3.00 (0.65)

[a]IQR, Interquartile range, difference between the 25th and 75th percentile.

Table 1: **Demographics of maternal and infant study participants.**

deaths (3.9%) occurred with 3 (congenital anomaly and pneumonia, neonatal anoxia, prematurity) in the Tdap group and 2 (acute respiratory infection, prematurity, 3.0%) in the Td group. None of the events reported in either group were determined to be related to study product. Additional details regarding these events can be found in the Supplementary Material (pg. 18).

Immunogenicity outcomes

One month after vaccination, women in the Tdap group had higher GMCs of anti-PT levels when compared to those in the Td group (90.0 IU/ml vs 10.4 IU/ml) (Table 3). Antibodies to FHA and PRN were also significantly higher in the Tdap group with GMCs of 545.3 IU/ml vs 29.5 IU/ml and 255.3 IU/ml vs 4.7 IU/ml and ratios of 18.5 (14.0–24.3) and 54.2 (35.6–82.4), respectively. At the time of delivery, the GMCs of anti-PT, anti-FHA and anti-PRN, though lower, remained significantly higher among women who received Tdap compared to those who received Td. At 6 months after delivery, 65 (48.9%) women in the Tdap and 33 (49.2%) in the Td group provided samples (Fig. 2). The GMCs and ratios had decreased further in the women receiving Tdap but remained significantly greater than the levels measured in the Td group. Anti-FIM2/3 levels remained largely unchanged throughout the maternal follow-up period. The anti-TT GMC was significantly greater in the Td group than in the Tdap group at one month after vaccination (6.6 IU/ml vs 10.4 IU/ml) and at delivery (3.3 IU/ml vs 4.6 IU/ml) with Tdap:Td ratios of 0.6 (0.5–0.8) and 0.7 (0.6–0.9), respectively. Six months after delivery, the difference was no longer significant. Anti-DT GMCs were similar in both maternal groups throughout the follow up period (Table 3).

At birth, the GMC of anti-PT levels measured in the infants was 55.4 [46.2–66.6] IU/ml in the Tdap group,

	Tdap					Td				
	N[a] (%)	Any severity	Mild	Moderate	Severe	N[a] (%)	Any severity	Mild	Moderate	Severe
Maternal										
N[b]	133					67				
Local reactogenicity events	9 (6.8)	9	9	0	0	10 (14.9)	12	12	0	0
Systemic reactogenicity events	0 (0.0)	0	0	0	0	4 (6.0)	4	4	0	0
Unsolicited adverse events	26 (19.5)	29	5	9	15	11 (16.4)	15	1	8	6
Pregnancy, puerperium, and perinatal conditions[c]	19 (14.3)	21	0	6	15	8 (11.9)	8	0	3	5
Serious adverse events[d]	20 (15.0)	22	0	7	15	10 (15.1)	10	0	5	5
Infant										
N	126					66				
Any adverse event	23 (18.2)	38	1	27	10	7 (10.6)	9	0	7	2
Infections and infestations	14 (11.1)	19	0	15	4	4 (6.0)	4	0	3	1
Perinatal conditions	8 (6.3)	8	0	6	2	4 (6.0)	4	0	3	1
Respiratory, thoracic and mediastinal disorders	2 (1.6)	2	0	0	2	1 (1.5)	1	0	1	0
Congenital, familial, and genetic disorders	2 (1.6)	4	1	1	2	0 (0.0)	0	0	0	0
Gastrointestinal disorders	2 (1.6)	2	0	2	0	0 (0.0)	0	0	0	0
Nervous system disorders	1 (0.8)	1	0	1	0	0 (0.0)	0	0	0	0
Metabolism and nutrition disorders	1 (0.8)	1	0	1	0	0 (0.0)	0	0	0	0
Skin and subcutaneous disorders	1 (0.8)	1	0	1	0	0 (0.0)	0	0	0	0
Serious adverse events[d]	13 (10.3)	18	0	8	10	6 (9.0)	8	0	6	2

Tdap, tetanus toxoid, reduced diphtheria toxoid and acellular pertussis adsorbed vaccine; Td, tetanus and diphtheria toxoids adsorbed vaccine. [a]N indicates the number of participants in each group who experienced the indicated events with any severity. [b]N indicates the number of participants in each group. [c]Includes a subset of all adverse events that were recorded among maternal participants. The remainder of events can be found in the Supplemental Material, pg 19. [d]Includes a subset of all adverse events that were determined to be serious.

Table 2: **Summary of maternal and infant unsolicited adverse events by organ class, severity and treatment group.**

Population	Time point	PT			FHA			PRN			TT			DT			FIM 2/3		
		Tdap[a]	Td[a]	Tdap to Td ratio	Tdap[a]	Td[a]	Tdap to Td ratio	Tdap[a]	Td[a]	Tdap to Td ratio	Tdap[a]	Td[a]	Tdap to Td ratio	Tdap[a]	Td[a]	Tdap to Td ratio	Tdap[a]	Td[a]	Tdap to Td ratio
Maternal	Pre -vaccination	9.1 (7.5, 11.1) (N = 130)	9.8 (7.3, 13.1) (N = 66)	0.9 (0.7, 1.3)	28.6 (24.4, 33.6) (N = 130)	27.1 (21.5, 34.2) (N = 66)	1.1 (0.8, 1.4)	5.6 (4.4, 6.9) (N = 130)	4.6 (3.5, 6.0) (N = 66)	1.2 (0.8, 1.8)	1.3 (1.0, 1.7) (N = 130)	1.3 (0.9, 1.9) (N = 66)	1.0 (0.6, 1.5)	0.2 (0.1, 0.2) (N = 130)	0.2 (0.1, 0.2) (N = 66)	1.0 (0.7, 1.6)	20.6 (15.8, 26.8) (N = 130)	22.3 (15.7, 31.6) (N = 66)	0.9 (0.6, 1.4)
	One month after vaccination	90.0 (76.8, 105.6) (N = 129)	10.4 (7.8, 13.9) (N = 66)	8.7 (6.2, 12.0)	545.3 (463.6, 641.4) (N = 129)	29.5 (23.7, 36.8) (N = 66)	18.5 (14.0, 24.3)	255.3 (186.4, 349.9) (N = 129)	4.7 (3.6, 6.2) (N = 66)	54.2 (35.6, 82.4)	6.6 (5.8, 7.4) (N = 129)	10.4 (8.8, 12.2) (N = 66)	0.6 (0.5, 0.8)	1.3 (1.1, 1.6) (N = 129)	1.5 (1.1, 2.0) (N = 66)	0.9 (0.6, 1.3)	31.8 (25.1, 40.2) (N = 129)	21.9 (15.5, 30.9) (N = 66)	1.5 (1.0, 2.2)
	Delivery	47.0 (40.1, 55.1) (N = 127)	10.1 (7.4, 13.6) (N = 64)	4.7 (3.3, 6.6)	321.5 (275.0, 375.8) (N = 127)	30.6 (24.8, 37.7) (N = 64)	10.5 (8.1, 13.7)	164.6 (121.0, 224.1) (N = 127)	5.1 (3.7, 7.1) (N = 64)	32.0 (20.6, 49.7)	3.3 (2.9, 3.8) (N = 127)	4.6 (3.9, 5.5) (N = 64)	0.7 (0.6, 0.9)	0.8 (0.6, 0.9) (N = 127)	0.9 (0.6, 1.2) (N = 64)	0.9 (0.6, 1.2)	26.3 (21.0, 33.0) (N = 127)	20.1 (14.3, 28.2) (N = 64)	1.3 (0.9, 1.9)
	6 months after delivery	40.9 (33.3, 50.2) (N = 65)	12.2 (8.2, 18.2) (N = 33)	3.3 (2.1, 5.2)	259.0 (205.3, 326.6) (N = 65)	34.9 (24.7, 49.3) (N = 33)	7.4 (5.0, 11.1)	97.1 (61.5, 153.5) (N = 65)	5.1 (3.5, 7.6) (N = 33)	18.9 (10.4, 34.2)	2.9 (2.3, 3.6) (N = 65)	3.8 (3.1, 4.5) (N = 33)	0.8 (0.6, 1.0)	0.6 (0.5, 0.9) (N = 65)	0.9 (0.6, 1.4) (N = 33)	0.7 (0.4, 1.2)	28.6 (20.0, 40.9) (N = 65)	19.8 (11.7, 33.4) (N = 33)	1.4 (0.8, 2.7)
Infant	Birth	55.4 (46.2, 66.6) (N = 124)	7.9 (5.4, 11.5) (N = 64)	7.0 (4.6, 10.7)	387.5 (327.9, 457.9) (N = 124)	28.4 (22.2, 36.3) (N = 64)	13.7 (10.2, 18.3)	184.5 (130.6, 260.6) (N = 124)	4.0 (2.7, 5.9) (N = 64)	46.4 (26.6, 81.0)	4.1 (3.5, 4.8) (N = 124)	5.9 (5.0, 7.0) (N = 64)	0.7 (0.6, 0.9)	0.8 (0.7, 1.0) (N = 124)	0.9 (0.7, 1.3) (N = 64)	0.9 (0.6, 1.3)	23.9 (17.8, 32.0) (N = 124)	15.2 (9.8, 23.8) (N = 64)	1.6 (0.9, 2.6)
	Prior to receipt of first dose of DTwP (~6 weeks of age)	21.0 (17.3, 25.5) (N = 114)	4.3 (3.0, 6.2) (N = 59)	4.8 (3.2, 7.3)	143.5 (121.8, 169.1) (N = 114)	13.3 (10.1, 17.6) (N = 59)	10.8 (8.0, 14.5)	72.6 (51.7, 101.9) (N = 114)	1.8 (1.3, 2.7) (N = 59)	39.5 (24.0, 65.0)	1.4 (1.2, 1.6) (N = 114)	2.0 (1.7, 2.4) (N = 59)	0.7 (0.5, 0.8)	0.3 (0.2, 0.4) (N = 114)	0.3 (0.2, 0.4) (N = 59)	1.0 (0.7, 1.5)	9.5 (7.1, 12.7) (N = 114)	6.9 (4.5, 10.4) (N = 59)	1.4 (0.8, 2.3)
	One month after receipt of first dose of DTwP (~10 weeks of age)	15.0 (11.4, 19.7) (N = 58)	5.1 (3.3, 8.1) (N = 32)	2.9 (1.8, 4.8)	89.4 (70.7, 113.2) (N = 58)	8.7 (6.2, 12.3) (N = 32)	10.2 (6.9, 15.2)	47.1 (33.2, 66.8) (N = 58)	4.5 (3.1, 6.6) (N = 32)	10.4 (6.1, 17.9)	0.8 (0.6, 0.9) (N = 58)	1.1 (0.9, 1.3) (N = 32)	0.7 (0.5, 1.0)	0.2 (0.1, 0.3) (N = 58)	0.2 (0.1, 0.3) (N = 32)	1.1 (0.6, 2.0)	10.9 (7.8, 15.3) (N = 58)	6.8 (4.8, 9.7) (N = 32)	1.6 (1.0, 2.7)
	One month after receipt of last dose of DTwP (~18 weeks of age)	20.2 (13.7, 29.9) (N = 50)	77.2 (32.2, 184.8) (N = 25)	0.3 (0.1, 0.7)	46.2 (37.8, 56.4) (N = 50)	22.5 (15.9, 31.7) (N = 25)	2.1 (1.4, 3.0)	48.6 (34.9, 67.8) (N = 50)	80.2 (52.2, 123.1) (N = 25)	0.6 (0.3, 1.1)	0.9 (0.6, 1.2) (N = 50)	1.5 (0.9, 2.4) (N = 25)	0.6 (0.3, 1.0)	0.2 (0.2, 0.3) (N = 50)	0.4 (0.2, 0.6) (N = 25)	0.6 (0.3, 1.1)	254.0 (153.3, 420.6) (N = 50)	517.6 (292.2, 916.8) (N = 25)	0.5 (0.2, 1.1)
	6 months of age	17.3 (12.8, 23.4) (N = 63)	67.1 (35.5, 126.7) (N = 32)	0.3 (0.1, 0.5)	23.9 (19.2, 29.8) (N = 63)	20.7 (14.2, 30.2) (N = 32)	1.2 (0.8, 1.7)	28.4 (21.6, 37.3) (N = 63)	39.1 (28.2, 54.2) (N = 32)	0.7 (0.5, 1.1)	0.8 (0.6, 1.1) (N = 63)	1.0 (0.7, 1.4) (N = 32)	0.9 (0.5, 1.4)	0.2 (0.1, 0.2) (N = 63)	0.1 (0.1, 0.2) (N = 32)	1.2 (0.8, 2.0)	274.3 (191.7, 392.6) (N = 63)	465.6 (316.7, 684.6) (N = 32)	0.6 (0.3, 1.0)

GMC (95% confidence interval); PT, Pertussis toxin; FHA, Filamentous hemagglutinin; PRN, Pertactin; TT, Tetanus toxin; DT, Diphtheria toxin; FIM 2/3, Fimbriae 2/3; N, number of participants in each cell who provided a blood sample. [a]Units = IU/ml.

Table 3: **Serum IgG ELISA geometric mean concentration (GMC) results by antigen, time point, and treatment group, maternal and infants modified intent-to-treat population.**

significantly higher than the GMC of 7.9 [5.4–11.5] IU/ml in the Td group, and with a ratio of 7.0 (4.6–10.7) (Table 3 and Fig. 3). There were similar findings when measuring anti-FHA and anti-PRN levels. At 6 weeks of age, prior to receiving the first dose of DTwP, the GMCs of anti-PT, anti-FHA and anti-PRN antibodies of infants in the Tdap group were lower than at birth but remained significantly higher than among infants whose mothers had received Td. One month after the first dose of DTwP, infants in the Tdap group had GMCs of anti-PT, anti-FHA and anti-PRN that were lower than at the previous timepoint but remained significantly higher than the levels measured in infants in the Td group. However, one month after the last dose of DTwP, the GMCs of anti-PT and anti-PRN in the infants born in the Tdap group were lower compared to those of the Td group and the ratios dropped to less than 1. At this time point, the GMC of anti-PT in infants born to mothers in the Tdap group was lower compared to the Td group (20.2 [13.7–29.9] IU/ml vs 77.2 [32.2–184.8] IU/ml). Though the GMCs of anti-FHA in the Tdap group remained significantly higher than in the Td group, the ratio of anti-FHA levels had dropped significantly. At 6 months of age, 63 (50.8%) infants in the Tdap and 32 (50.0%) in the Td group provided samples (Fig. 2). The GMCs of anti-PT and anti-PRN levels were lower in the Tdap group, though no longer significantly so, and the anti-FHA levels were no longer significantly higher in the Tdap group compared to the Td group. The anti- PT GMCs were 17.3 [12.8–23.4] IU/ml and 67.1 [35.5–126.7] IU/ml in Tdap and Td groups, respectively. The GMC of anti-FIM2/3 antibodies were similar between groups until one month after the last dose of DTwP (Fig. 3).

At birth, like their mothers, GMCs of the anti-TT levels were significantly higher in infants born in the Td group than in the Tdap group (5.9 [5.0–7.0] IU/ml vs 4.1 [3.5–4.8] IU/ml) (Table 3 and Fig. 2). Over the 6-month infant follow up period, the GMCs in the Td group were consistently greater than in the Tdap group and all levels were greater than 0.01 IU/ml at all time-points in both groups. Anti-DT GMCs were similar in both groups of infants throughout the follow up period.

There was no numeric difference in anti-PT GMCs in mothers at delivery and infants at birth within each treatment group with respect to the number of weeks of gestation at the time of study vaccination, although the GMC of those vaccinated at 22–26 weeks gestation was greater than the others (Table 4). In all gestational age groups, the GMCs in the Tdap group were greater than in the Td group. The ratio of maternal PT antibodies at

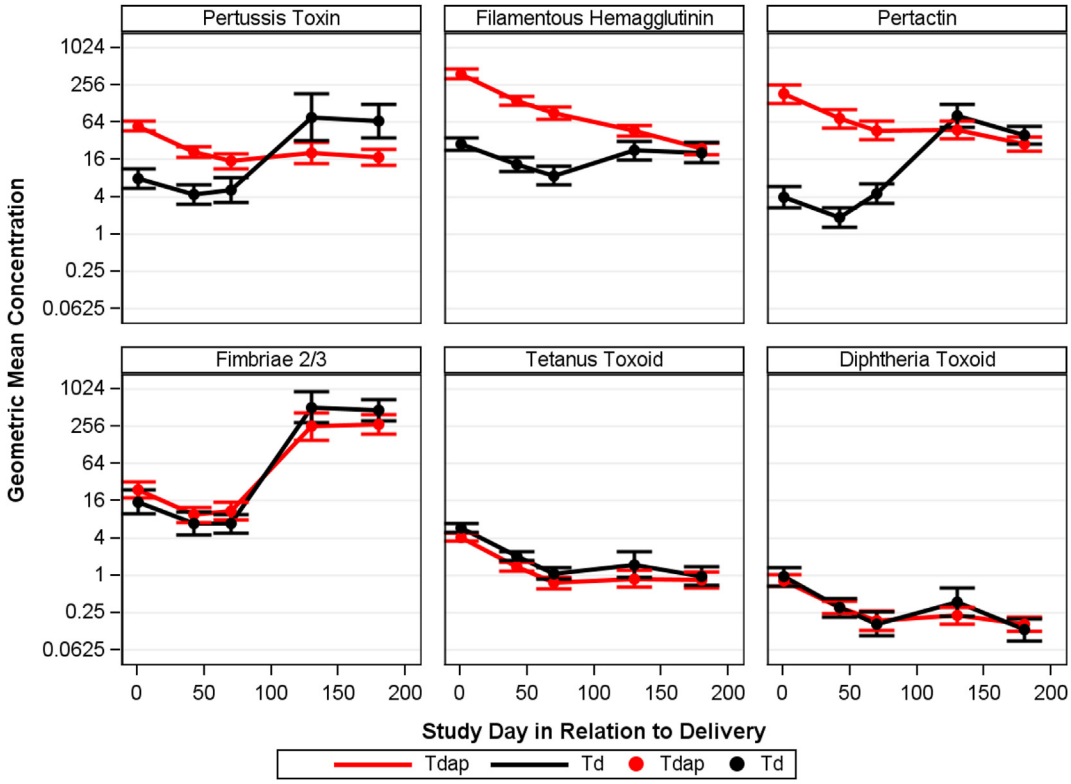

Fig. 3: **Geometric mean concentrations of antibody to pertussis, tetanus and diphtheria antigens among infants by study day and by maternal vaccine group.**

Vaccine		Tdap (N = 130)			Td (N = 66)			Tdap to Td ratio		
Week of gestation		14–17 Weeks (N = 57)	18–21 Weeks (N = 41)	22–26 Weeks (N = 32)	14–17 Weeks (N = 35)	18–21 Weeks (N = 12)	22–26 Weeks (N = 19)	14–17 Weeks	18–21 Weeks	22–26 Weeks
Maternal antibody at delivery	n	55	41	31	33	12	19	–	–	–
	GMC IU/ml (95% CI)	46.0 (36.1, 58.7)	43.4 (31.8, 59.3)	54.1 (40.3, 72.6)	10.3 (6.6, 16.0)	12.7 (5.4, 29.8)	8.4 (4.9, 14.2)	4.5 (2.7, 7.4)	3.4 (1.7, 6.9)	6.5 (3.8, 11.1)
	p-value[a]	–	–	–	–	–	–	<0.0001	0.0010	<0.0001
Infant antibody at birth	n	54	40	30	33	12	19	–	–	–
	GMC IU/ml (95% CI)	52.1 (39.4, 68.8)	49.6 (34.8, 70.7)	72.0 (51.1, 101.3)	7.7 (4.5, 13.3)	11.3 (4.3, 30.1)	6.5 (3.2, 13.3)	6.8 (3.7, 12.4)	4.4 (2.0, 9.8)	11.1 (5.1, 24.1)
	p-value[a]	–	–	–	–	–	–	<0.0001	0.0006	<0.0001
Maternal at delivery to infant at birth ratio	n	54	40	30	33	12	19	–	–	–
	GMR (95% CI)	1.2 (1.1, 1.2)	1.2 (1.1, 1.3)	1.3 (1.2, 1.4)	0.7 (0.6, 0.9)	0.9 (0.7, 1.1)	0.8 (0.6, 1.0)	–	–	–

Tdap, tetanus toxoid, reduced diphtheria toxoid and acellular pertussis adsorbed vaccine; Td, tetanus and diphtheria toxoids adsorbed vaccine; GMC, Geometric mean concentration; GMR, Geometric mean ratio; N, Number of subjects in the infant modified intent to treat population in the treatment group; n, Number of subjects with results available at time point. [a]p-value is based on t-test on log-transformed ELISA titres and compares the GMCs of the maternal and infant antibody levels in the Tdap vs Td group at each gestational age stratum. Note, p-values are not adjusted for multiple comparisons and should be interpreted accordingly.

Table 4: **Summary of maternal and infant serum IgG antibody titres to pertussis toxin by maternal gestational age at vaccination and by treatment group.**

delivery to infant PT antibodies at birth were greater than 1 for all gestational age groups in the Tdap group but were less than 1 in the Td group.

Discussion

The WHO and the Global Pertussis Initiative recognise vaccination against pertussis in pregnancy as the most effective available means of protecting infants too young for primary vaccination.[1,20] In this study of Tdap vs Td vaccine administered to pregnant women in Mali, reactogenicity was similar in the two vaccine groups and confirms observations in other populations.[10,21,22] Though there were more foetal deaths noted in the Tdap group, the causes of death were consistent with known complications of pregnancy in this low resource population in Mali. Recognising the limitations of sample size, the significance of this difference is unclear. The remaining serious events and maternal and infant deaths were similar in the two vaccine groups. As Td is routinely given to pregnant women in Mali, the substitution with Tdap should be programmatically acceptable and feasible.

To be effective, a maternal immunisation strategy relies on antibody transfer from the mother to the foetus so that at birth the infant benefits from that antibody. In this study, the infants of mothers who received Tdap during pregnancy were born with high levels of antibody to pertussis antigens with ratios of maternal to infant anti-PT levels at birth that were greater than 1. Gestational age at vaccination may impact the amount of antibody transferred through the placenta and the effectiveness of this intervention.[11] In our study, mothers vaccinated with Tdap in the second trimester (median 19 weeks gestation) conferred pertussis antibodies to their infants with high levels detected at birth and these titres remained statistically higher in the Tdap group until 10 weeks of age, prior to the second dose of DTwP. GMCs at these timepoints were similar between those vaccinated earlier and later in the second trimester (Table 4). While there is no established correlate of protection for pertussis vaccines, PT is known to contribute to the clinical manifestations of severe pertussis in infants[23] and an anti-PT level of 10 IU/ml has been used in other studies to distinguish risk categories.[24] Mean PT antibody levels remained higher than 10 IU/ml in the Tdap group through the 6-month infant visit, while mean PT antibody levels were less than 10 IU/ml in the Td group through at least the 10-week time point. Given that the greatest burden of pertussis cases and deaths occur in those less than 2 months of age,[1] our results suggest that maternal vaccination with Tdap would benefit these young infants.

The beneficial effects to the infant of maternally-derived transplacental antibody early in life must be balanced with any detrimental effects on primary infant responses to pertussis-containing vaccines.[25] In our study, four weeks after receipt of the third dose of DTwP and at 6 months of age, PT antibody levels were higher in the infants born to Td mothers than in infants born to Tdap mothers, consistent with a blunted immune response to primary vaccination in the Tdap group. The pattern of blunted infant immune responses to other pertussis antigens was less consistent. The anti-PRN and anti-FHA GMCs did not increase after completion of the primary series. Anti-PRN levels followed a similar pattern to anti-PT levels, being higher at birth, 6 and 10 weeks in the Tdap group and higher at later timepoints in the Td group, although the latter comparisons were not statistically significant. Anti-FHA levels remained higher in the Tdap as compared to the Td group through

the 18-week timepoint and were similar in the two groups at 6 months of age. Our findings are consistent with other studies showing blunted immune responses to primary vaccination in infants whose mother was vaccinated in pregnancy, with the effect being more pronounced in infants receiving whole-cell pertussis vaccines.[10,16,26–29]

In Mali and similar countries, primary vaccination occurs at 6-, 10- and 14-weeks of life and no booster dose of DTwP is administered. While it is reassuring that mean PT antibody levels remained higher than 10 IU/ml in the Tdap group through the 6-month infant visit, the lack of a booster dose raises concern for susceptibility to pertussis in later infancy. Booster vaccines in the second year of life can partially overcome previously blunted immune responses.[10,30,31] A study in Australia, Canada and Europe found lower post-booster antibodies to FHA and PT but not PRN when mothers had received Tdap in pregnancy compared to placebo[31] and in Belgium, post-booster responses to PT were lower.[32] Notably, after implementation of maternal pertussis vaccination in Australia, decreases in neonatal pertussis were observed without increases in pertussis disease in the second year of life.[33] Whether this finding would hold in a setting without a booster dose is uncertain, and supports the need for monitoring of pertussis epidemiology in such settings.

As of March 2022, Mali remains one of 12 countries that has not eliminated maternal and neonatal tetanus.[34] Standard of care is to administer a dose of a WHO-prequalified tetanus-containing vaccine to pregnant women at the first antenatal visit. Tdap contains a lower dose of tetanus toxoid than Td and it was important to ensure that this did not affect the ability to achieve protective levels of anti-TT at delivery and birth. That infants in both groups in our study had anti-TT GMCs above the protective level of tetanus antibody (>0.01 IU/ml)[35] through the 6-month time point is reassuring and supports the current maternal vaccine policy. Nevertheless, TT antibody titres were higher in mothers who received Td vaccine and in their infants. By 6 months of age, anti-TT levels were similar and lower than at birth in both groups of infants. Notably, infants in Mali receive a dose of meningococcal serogroup A vaccine conjugated to tetanus toxoid at 9 months of age, with a resulting boost in tetanus antibody.[36] However, these children may remain vulnerable to diphtheria or pertussis in later years of childhood.

While this study details the antibody kinetics of maternal pertussis immunisation in Mali and similar settings where whole-cell pertussis vaccines are used in infancy, the COVID-19 pandemic interrupted our ability to complete in-person visits with corresponding sample collection. As a result, specimen collection did not occur for nearly half of participants at the 6-month visit. This time point is particularly important to understand the susceptibility of the infants after completion of the primary series of infant vaccines. While the anti-PT levels were significantly higher in the Td group than the Tdap group at the 6-month time point, the reduced number of samples affected robustness of comparisons for other antigens at this time point. Though there are data suggesting that responses to other antigens included in the primary vaccination schedule may be blunted following maternal immunisation with Tdap,[37] those assessments were beyond the scope of this study. The decrease in the GMC of anti-FIM2/3 antibodies after the last dose of DTwP in the Tdap group suggests that this is worth investigating.

Our study demonstrates that maternal pertussis vaccination in the second trimester achieves putative protective levels of anti-PT in early infancy—the period when most deaths from pertussis occur. While there is a blunting effect on the antibody responses to primary pertussis immunisation later in infancy, the clinical significance is unclear. A later timing of infant immunisation could mitigate the blunting effects of maternal antibody and yield higher infant responses to DTwP and likely other, infant vaccines.[38] Moreover, the feasibility of such a delay would have to be accompanied by a timely and high coverage maternal immunisation program.[39] Further, recent additions to immunisation schedules in sub-Saharan Africa in the second year of life, including second dose measles-containing vaccine, typhoid conjugate vaccine and malaria vaccine, may provide a platform for including booster doses of DTwP vaccine which may be needed to ensure that children are protected in the second year of life. Ultimately, the decision on whether to introduce Tdap during pregnancy must consider the epidemiology of pertussis in the particular setting, and the feasibility, effectiveness, and cost of the intervention. Studies to assess durability of immune responses, and the potential need for booster doses, are warranted.

Contributors

MDT, SOS, ER, KLK and KMN participated in the study design. FCH, FD, AT and SOS participated in data collection. SP, MW, and MP were responsible for laboratory testing. EH, MM, SS, JAP and KMN participated in data analysis and interpretation. FCH, MDT and KMN participated in the literature review and primary manuscript writing. FCH, MDT and KMN haver verified the underlying data. All authors contributed to revision of the manuscript and have read and approved the final version.

Data sharing statement

This trial was conducted in accordance with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. This manuscript which includes study data (in aggregate) will be submitted to the digital archive PubMed Central (http://www.ncbi.nlm.nih.gov/pmc/) within 12 months after acceptance for publication.

The primary and secondary study results and supporting safety and immunogenicity data are publicly available on ClincialTrials.gov, along with copies of the study protocol, informed consent form, and Statistical Analysis Plan. Deidentified, individual-level data can be provided upon request.

Declaration of interests
We declare no competing interests except for KLK, who reports funding to conduct this research from NIAID to her institution.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102556.

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