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Bacille Calmette-Guérin-specific IgG titres among infants born to mothers with active tuberculosis disease in Uganda

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Abstract

Background Infants born to mothers with active tuberculosis disease (ATB) are at risk of poor clinical outcomes such as low birth weight and perinatal mortality. However, little is known about the influence of maternal ATB exposure on their vaccine responses during infancy. The study explored how maternal ATB affects infants' vaccine responses, hypothesising reduced responses to *Bacille Calmette-Guérin* (BCG) and other infant vaccines.

Methods This was a case-control study with a longitudinal component of infants born to mothers with bacteriologically confirmed ATB (cases) and infants born to mothers without ATB (controls) carried out between September 2021 and June 2022. Quantitative BCG, diphtheria, tetanus, and measles-specific IgG ELISA assays were performed on infant plasma harvested from lithium-heparin blood collected on first encounter after birth (0), at 3, 6, and 9 months. We used prism v10.1.2, mixed-effects modelling, and Tukey's multiple comparison testing to determine mean differences (MD) between the cases and controls at all time points.

Results Exposed infant cases had reduced IgG titres to BCG at baseline compared to the controls ($p=0.032$), with a mean of 125.8 vs. 141.1 IU/mL, respectively. This difference was, however, not sustained at the other time points. Similarly, we demonstrated trends towards reduced responses to tetanus, diphtheria, and measles vaccines among infant cases at baseline and three months. However, the trend was not sustained at months six and nine. The mean titres for tetanus at baseline and 3 months for cases versus controls are 1.744 vs. 2.917 IU/mL ($p<0.0001$) and 1.716 vs. 2.344 IU/mL ($p=0.018$), respectively. The mean titres for diphtheria at 3 months for cases versus controls were 0.022 vs. 0.075 IU/mL ($p=0.006$), respectively.

Conclusion We have demonstrated that maternal TB disease influences vaccine responses to BCG and other infant vaccines. This has implications for increased risk of childhood TB and other preventable diseases.

Clinical trial number Not applicable.

Keywords Active tuberculosis, Mothers, Infants, Vaccine response

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Background

The incidence of Tuberculosis (TB) disease among people aged below 30 years of age has increased, hence increasing the number of childbearing women contracting the disease [1]. The TB burden in pregnancy globally is estimated to be 216,500 cases annually, with a threefold increased risk of TB in this population [2]. This may be due to immunological changes mediated by pregnancy that cause a decline of T-helper (Th)-1 cell-mediated immune response, which increases susceptibility to TB [3, 4]. Mother-to-child transmission of TB may occur *in utero* through hematogenous spread via the umbilical vein and aspiration or swallowing of infected amniotic fluid [5, 6]. TB disease in pregnancy leads to poor maternal and foetal outcomes such as preterm birth, low birth weight [7], perinatal death, congenital anomalies, small for gestational age, foetal distress, low Apgar scores, and rare congenital tuberculosis [8].

There is limited data on the immune responses to *Bacille Calmette-Guérin* (BCG) and other vaccines of infants born to mothers with active TB (ATB). Vaccination with BCG has been reported to be associated with reduced infant mortality [9, 10]. However, it remains unclear whether this is true for all populations, including infants born to mothers with active tuberculosis. A study by Lubyayi et al., 2020 revealed that maternal latent TB infection (LTBI) status does not affect the infants' response to BCG-vaccine [11]. On the other hand, Mawa et al., 2015 reported a decrease in purified protein derivative (PPD)-specific responses among infants born to mothers with latent tuberculosis infection at one week and six- weeks following vaccination with BCG compared to the control group [12]. Both studies explored the impact of maternal latent TB on infant vaccine responses; however, in this study, we assessed vaccine responses among infants born to active TB mothers and compared them with infants born to TB-uninfected mothers. We considered it necessary also to determine if exposure to TB disease influenced the other infant vaccines to pave the way for possible public health-related interventions, given that HIV alone has been implicated in causing a reduced response to vaccines among infants [13].

This study determined the IgG titre responses to BCG, diphtheria, tetanus, and measles vaccines in infants born to mothers with and without active TB disease at baseline, three, six, and nine months of follow-up.

Methods

Study design and population

This was a case-control study with a longitudinal component. The study enrolled 35 women with bacteriologically confirmed active TB as cases and 33 women without TB as controls matched for maternal and gestational age from antenatal (ANC) and postnatal (PNC) clinics at three major health facilities in Kampala, Uganda: Kasangati Health Center IV, Kisenyi Health Center IV, and Kawempe National Referral Hospital. However, we considered 25 cases (infants born to mothers with active tuberculosis disease) and 25 controls (infants born to mothers without active tuberculosis disease) in our experiments, whose numbers also decreased in successive follow-up months. Mothers consented to enrol their infants in the study and were followed up for nine months. These infants donated up to six millilitres of blood in lithium-heparin tubes at different time points, from which plasma was harvested and stored at -20℃ in a freezer at the Immunology laboratory of Makerere University College of Health Sciences (MakCHS). The baseline visit (V0) marked the visit of the first encounter with infants aged less than a month (cases, $n = 19$ versus controls, $n = 15$). The V1 marked a visit at three months (cases $n = 15$ versus controls $n = 14$), V2 at six months (cases $n = 12$ versus controls $n = 8$), and V3 at 9 months (cases $n = 8$ versus controls $n = 4$). Vaccine schedules included BCG at birth; pentavalent vaccine [tetanus-diphtheria-pertussis-hepatitis B-haemophilus influence type B (DPT-HEPB-HIB1)] at 6, 10, 14 weeks; and measles at 9 months.

Laboratory methods

Heparinised blood was layered over Ficoll-Paque in a ratio of 1:2 under a biosafety cabinet in a 15 ml Falcon tube. This was spun in a centrifuge at 1800 rpm for 30 min to separate plasma and PBMC from red blood cells. Plasma was harvested using a pipette and was stored at -20ºC. All assays for each vaccine were optimised to achieve a suitable dilution factor. Archived available plasma samples were retrieved from a -20ºC freezer and transferred to the fridge at the temperature of 4℃ overnight. They were then retrieved from the refrigerator and thawed with the ELISA kits at room temperature (25℃) for 1 h. Plasma samples were vortexed to achieve uniform mixing, and 50 µl were loaded into designated wells, in addition to standards and blanks, of the 96-well ELISA plates. The human IgG-specific ELISA assays were performed to determine plasma IgG titres of BCG, diphtheria-tetanus, and measles vaccine responses using the human BCG, diphtheria, tetanus and measles IgG ELISA kits following the manufacturer's instructions. The absorbance at 450/620 nm was measured using the Gen 5 software version 2.71.2 for the ELISA reader (Synergy LX multimode reader). Detailed procedures are available in Additional File 1.

Data analysis and management

Optical densities (OD) from the ELISA were converted to concentrations using the Gen 5 software version 2.71.2 and then exported to Excel. Using Excel, the data was

cleaned and grouped as cases versus controls at baseline, 3, 6, and 9 months. Data was statistically analysed in GraphPad Prism v9.5.1 using the mixed model effect analysis with Tukey's multiple comparisons test. Means, mean difference (MD), and standard error of difference (SE) for both cases and controls were computed at all time points. A simple linear regression analysis was performed on the relationship between birth weight, haemoglobin, and vaccine responses at all time points. The Mann-Whitney U-test was used to determine statistical differences in infant weights, age, and the mother's haemoglobin concentrations among both cases and controls. We measured maternal haemoglobin levels to assess the potential impact of maternal anemia on neonatal outcomes and vaccine responses as a pilot for another substudy. The chi-square test was also used to determine statistical differences in the gender of infants, and their maternal HIV status.

Results

Characteristics of the study participants

The median birth weight was significantly lower ($p = 0.029$) in infants born to mothers with ATB, 3.0 (2.1–3.2) compared to infants born to mothers without ATB, 3.4 (2.7–4.4), as shown in Table 1. The median maternal haemoglobin levels (g/dl) were significantly lower ($p = 0.033$) in cases, 11.2 (10.0-11.9) compared to controls, 13.0 (10.7–13.8). Other characteristics, such as age, gender, and maternal HIV status, were not different for both cases and controls.

BCG-specific IgG responses

The IgG titres were determined in plasma samples of the case infants versus the control infants. The samples were collected at V0, V1, V2, and V3, and the titres were compared at all time points. The IgG titres were strongly decreased in cases versus controls ($p = 0.032$) at V0. The mean for cases versus controls (IU/mL), mean difference (MD) 95% confidence interval (CI), p-value, and Standard Error (SE)] are shown in Table 2. This was followed by a gradual reduction of IgG titres among cases and controls at the rest of the time points: 3, 6, and 9 months ($p = 0.574/0.626/0.717$), respectively. These differences were, however, not significant, as demonstrated in Fig. 1 (A and B).

IgG vaccine responses to other vaccines

Tetanus-specific IgG responses

Infant cases had slightly lower IgG responses to tetanus at baseline compared to the controls ($p < 0.0001$)and this was followed by a significant decrease at 3 months ($p = 0.018$). The mean (IU/mL), mean difference (MD), 95% confidence interval (CI), p-value, and Standard Error (SE) are shown in Table 2. The trends showed a steep reduction in the responses among controls; however, the tetanus titres among cases increased gently up to 9 months, slightly surpassing the controls observed to fairly rebound at 9 months, as shown in Fig. 2 (A and B).

Diphtheria-specific IgG responses

Cases had strongly reduced IgG responses at 3 months of follow-up ($p = 0.0059$) compared to controls. The mean (IU/mL), mean difference (MD), 95% confidence interval (CI), p-value, and Standard Error (SE) are shown in Table 2. A sharp increase followed this in titres, which peaked at 6 months and then dropped at 9 months for controls. On the other hand, the responses for cases are steadily maintained from baseline up to the end of follow-up, as shown in Fig. 2(C and D). At months 6 and 9, the p values were $p = 0.8563$ and 0.8589, respectively. No difference was observed in the response to diphtheria at baseline ($p = 0.392$).

Measles-specific IgG responses

The trends showed that cases had a slightly higher response at all time points than controls, with the highest response shown at month 9. On the contrary, controls show waning titres between months 6 and 9. At baseline, 3, 6, and 9 months, the p values were: $p = 0.7402/0.9339/0.4409/0.5155$, respectively. These differences were, however, not statistically supported, as shown by Fig. 2(E and F). The mean (IU/mL), mean difference (MD), 95%

Table 1 Shows baseline participant characteristics

	Cases ($n = 25$)	Controls ($n = 25$)	*p*-value
Infants			
Weight (Kgs) [median (IQR)]	3.0 (2.1–3.2)	3.4 (2.7–4.4)	0.029
Age (weeks) [(median (IQR)]	7 (2–12)	12 (1–16)	0.445
Sex, Male/Female	8/12	8/12	0.999
Mothers			
Haemoglobin (g/dl) [median (IQR)]	11.2 (10-11.85)	12.95 (10.7-13.83)	0.033
Living with HIV, n (%)	7 (28%)	8 (32%)	0.467

A p-value less than 0.05 was considered statistically significant. Missing values for weight, age, sex, haemoglobin concentration, HIV status, and Antenatal versus postnatal care are 11, 12, 10, 10, 4, and 3, respectively

Table 2 Vaccine responses among cases and control at the different follow-up time points

Vaccine	Time Points	Cases Mean (IU/mL)	Controls Mean (IU/mL)	Mean Difference	95% CI	SE	*p*-value
BCG	Baseline (V0)	125.8	141.1	-15.3	-29.30 to -1.45	6.727	0.032
	Month 3 (V1)	122.6	128.2	-5.6	-25.77 to 14.56	9.862	0.574
	Month 6 (V2)	113.6	120.1	-6.5	-34.57 to 21.50	13.130	0.626
	Month 9 (V3)	116.8	99.4	17.4	-145.10 to 179.90	42.220	0.717
Tetanus	Baseline (V0)	1.744	2.917	-1.173	-1.647 to -0.699	0.226	< 0.0001
	Month 3 (V1)	1.716	2.344	-0.628	-1.139 to -0.119	0.248	0.018
	Month 6 (V2)	1.595	4.240	-2.645	-5.890 to 0.599	1.437	0.098
	Month 9 (V3)	1.713	2.267	-0.554	-10.880 to 9.778	0.912	0.649
Diphtheria	Baseline (V0)	0.042	0.062	-0.020	-0.066 to 0.027	0.022	0.392
	Month 3 (V1)	0.022	0.075	-0.053	-0.088 to -0.016	0.017	0.006
	Month 6 (V2)	0.045	0.040	0.005	-0.050 to 0.060	0.026	0.856
	Month 9 (V3)	0.063	0.054	0.009	-0.110 to 0.128	0.048	0.859
Measles	Baseline (V0)	1.759	1.599	0.160	-0.825 to 1.145	0.477	0.740
	Month 3 (V1)	1.582	1.624	-0.042	-1.068 to 0.984	0.505	0.934
	Month 6 (V2)	2.702	2.036	0.666	-1.115 to 2.447	0.844	0.441
	Month 9 (V3)	2.990	1.760	1.230	-3.300 to 5.759	1.757	0.516

Data was expressed as mean, mean difference, confidence interval, standard error of difference, and a p-value of less than 0.05 was considered statistically significant

Please note: Table 2 should be placed just after Table 1, but because it exceeds the required A4 page size, I have placed it here

Also, the following additional files have been added:

Additional file 1. This PDF file contains supplementary information on the procedure of protocols used to perform the experiments

Additional file 2. This PPT file shows regression analysis for the birthweight and haemoglobin concentrations of the infants versus the IgG responses to BCG, DPT, Tetanus, and Measles vaccines

Additional file 3. This CVS file shows the simple linear regression statistics for IgG responses versus the haemoglobin concentration of infants

Additional file 4. This CVS file shows the simple linear regression statistics for IgG responses versus the birth weight of infants

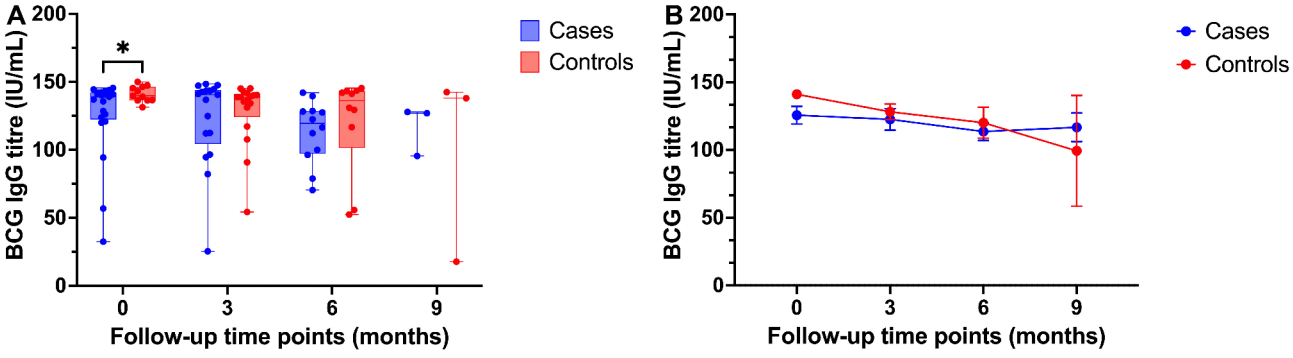

Fig. 1 (**A** and **B**). Plasma was used to perform ELISA using the Human BCG antibody ELISA kit. Two replicates of each sample were used for both case and control samples. The number of samples (n) for cases and controls at V0 was 19/15; at V1, $n = 15/15$; at V2, $n = 12/8$; and at V3, $n = 8/3$ respectively. Statistical differences were determined using mixed effects analysis and Tukey's multiple comparison tests. Statistical significance was determined at $p < 0.05$ and a 95% confidence level. * Implies a p-value less than 0.05

confidence interval (CI), P-value, and Standard Error (SE) are shown in Table 2.

Impact of birth weight on vaccine responses

In this study, we further grouped cases and controls as either normal or low birth weights (kgs) based on the World Health Organisation's guidelines, and infants with a birth weight lower than 2.5 kg were considered low birth weight. Normal birth weight ranged between 2.5 and 4.0 kg. BCG and tetanus-specific IgG titres for normal birth weight were lower among cases than controls. However, there was no difference in diphtheria and measles vaccine responses between low and normal birth weight infants, as shown in Fig. 3 (A, B, C, and D). A comparison of the vaccine responses to normal birthweight revealed that cases with normal birth weight had low responses to BCG ($p = 0.007$) and tetanus ($p = 0.004$) vaccines. No differences were observed in the comparison of normal birth weight with measles ($p = 0.055$) and diphtheria ($p = 0.093$) responses. The regression analysis also revealed that birth weight slightly affected BCG responses ($p = 0.06$); however, this was not statistically supported.

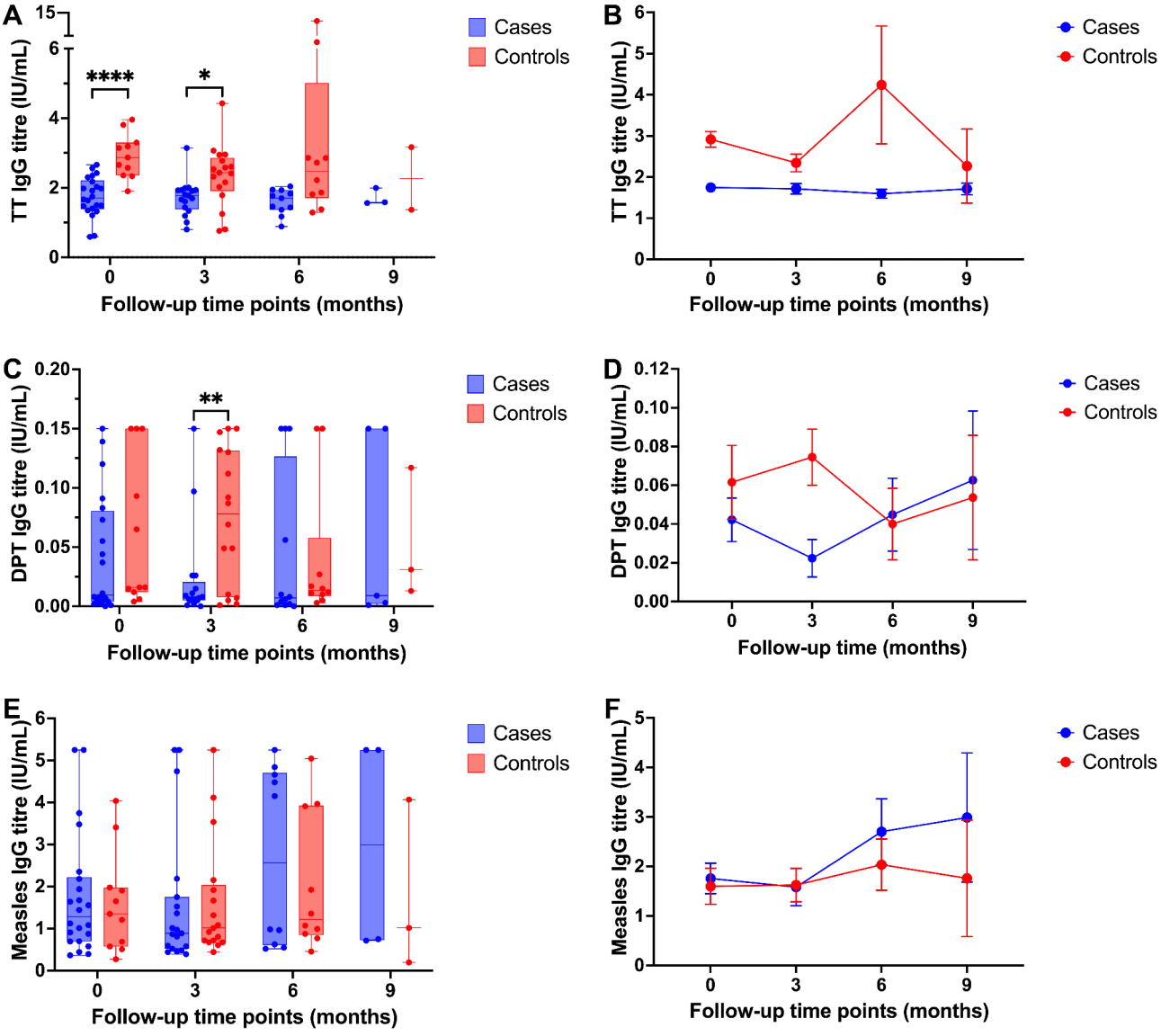

Fig. 2 (**A** and **B**). Stored plasma was used to perform ELISA using the Human Tetanus Toxoid Antibody IgG (TT-IgG) ELISA Kit. The number of cases versus controls used at each visit was V0 = 18/17, V1 = 15/11, V2 = 11/10, and V3 = 9/4, respectivelyFig. e 2 (**C** and **D**). plasma was then used to perform ELISA using the Corynebacterium diphtheriae toxin IgG ELISA kit. The number of cases versus controls at V0 = 20/14, V1 = 15/15, V2 = 13/7, and V3 = 8/4, respectivelyFig. e 2 (**E** and **F**). Plasma was used to perform ELISA using the Human Measles virus IgG antibody (MV-Ab-IgG) ELISA Kit. The number of cases versus controls used at V0 = 20/16, V1 = 18/12, V2 = 11/9, and V3 = 8/5, respectively. Statistical differences were determined using mixed effects analysis and Tukey's multiple comparison tests. Statistical significance was determined at $p < 0.05$ and a 95% confidence level. * and **** imply a p-value less than 0.05 and 0.0001, respectively. ** indicate a p-value less than 0.01

Discussion

Pregnancy modulates the immune response towards Th2-type response [14], increasing susceptibility to intracellular pathogens, including TB [15]. This study demonstrated that infants born to mothers with ATB have reduced BCG-specific IgG titres at baseline. Maternal tuberculosis disease potentially leads to the transfer of tuberculosis antigens to the foetus, resulting in an altered priming of the immune response [16]. The observed reduced BCG responses at baseline could, therefore, result in anergy induced by maternal antibodies; however, this remains to be explored. The responses remained relatively stable over time. The results further show that cases had slightly reduced responses at six months for BCG responses, unlike for Measles. These results contradict what Edwards, 2015 [17] reported: measles vaccine responses were reduced at six months, possibly due to passive maternal antibodies. On the other hand, Nabunya et al., 2020 reported that about 36% of infants are not breastfed beyond six months in Uganda [18]. This implies that the transfer of the antibodies through breast milk is reduced. Our results suggest the insufficiency in

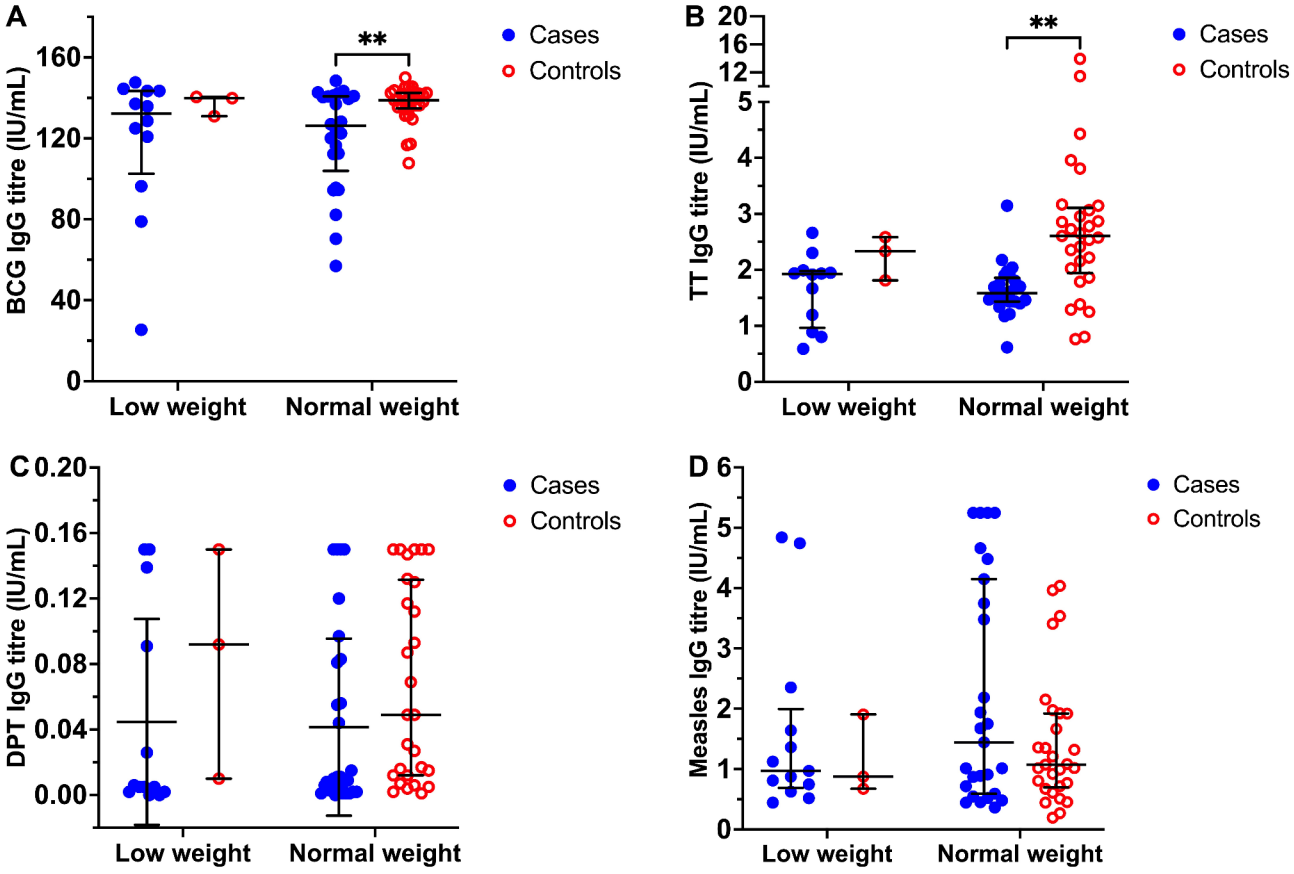

Fig. 3 (**A**, **B**, **C**, **D**). This figure shows a sub-analysis of IgG vaccine-specific responses for infants of low and normal birth weights. Mann-Whitney U test was used to determine the statistical differences. Data were expressed as median and interquartile ranges. ** indicate a p-value less than 0.01

responses to the BCG vaccine due to TB exposure. These findings show that maternal TB may impair the infants' immune responses to the BCG vaccine. We suggest that careful attention is taken to ensure that the infants exposed to TB develop protective immunity following vaccination to protect these infants from early-life infections and deaths from active TB.

In addition to BCG, the study reported a reduction in diphtheria-specific IgG-specific titres among cases at three months. Tetanus-specific IgG-specific vaccine responses were reduced at baseline and three months among cases compared to the controls. This data highlights that maternal TB disease indeed influences responses to vaccines among infants, and care should be taken to ensure that these exposed infants achieve protective immunity following vaccination. This will be aimed towards averting early-life infections and, consequently, potential infant deaths attributable to active TB. DPT and measles responses rebound after three months, shooting higher among cases than the controls at 6 and 9 months; however, the differences in fluctuations are not significant. On the other hand, tetanus responses for cases are relatively stable over time, indicating minimal responsiveness to the vaccine.

The observed decrease in the IgG-specific diphtheria vaccine responses is consistent with findings from similar studies. Abu-Raya et al., 2021 found lower IgG levels in children whose mothers had received the Tdap vaccine [19]. Due to the impact of TB in pregnancy, including the low birth weight of infants, vaccination tends to be delayed. When administered, low vaccine responses are more likely to occur [20], predisposing infants to developing vaccine-preventable diseases and experiencing severe or fatal disease outcomes. It has also been demonstrated that maternal *Mycobacterium tuberculosis* (*Mtb)* infection during pregnancy raises levels of immunoregulatory cytokines [21], which inhibit the infant's immunological response to vaccination. In addition, the diphtheria titres were generally low at baseline because fewer mothers receive diphtheria toxoid boosters in pregnancy, resulting in lower maternal anti-diphtheria IgG transfer.

The current study also reports decreased tetanus-specific IgG vaccine titres among cases. Because the vaccine is administered at six weeks [22], B cell priming could have been delayed. In addition, since pregnant women are vaccinated with tetanus toxoid [23], the maternal IgG that crosses the placenta is likely to induce anergy to the infant's immune system, thereby causing a dampened

immune response. Additionally, maternal tetanus toxoid vaccination during pregnancy and passive transplacental transfer of IgG could explain the observed relatively high baseline tetanus titres in some infants.

We measured measles-specific IgG at baseline, three, and six months to capture any maternal or incidental measles antibodies prior to the intended 9-month measles vaccination. As expected, we did not observe large increases in measles-specific IgG before the ninth month. Instead, we may have captured passive maternal titres and any possible subclinical measles exposure or immune modulation before the standard measles vaccine was administered [24]. Our 9-month measurement, coincident with the recommended measles vaccination, captured only an early post-vaccination window for most infants and would, therefore, not necessarily reflect the full magnitude of the post-vaccine response.

These findings highlight the need for improved vaccine strategies for infants exposed to TB and a better understanding of vaccine failures in specific populations. The effects of TB exposure are also seen with other vaccines like diphtheria and tetanus. With vaccine failure within a particular group of people, efforts need to be taken to identify more shortfalls of the existing vaccines and pave the way for effective vaccines possibly tailored to populations. On the other hand, revising the vaccine schedule to give booster doses of the BCG vaccine, given its protective benefits against infections other than tuberculosis among infants exposed to tuberculosis, would enormously contribute to the End TB strategy.

This study further highlights the impact of maternal TB on the birth outcomes of infants, especially low birth weight. Similar results were reported elsewhere [25, 26], affirming this outcome. Vaccination delays associated with low birth weight further hamper the health outcomes of these infants, contributing to lower responses to vaccines and increased vulnerability to infections [27]. We postulate that the effects of TB exposure are not only observed with low birth weight. Therefore, when assessing for TB exposure, infants with normal birth weight should not be overlooked. Moreover, the regression analysis revealed that the birth weight of the infants slightly affected BCG-specific IgG responses, as shown in additional file 2. Our results also revealed that the mothers to infant cases had low haemoglobin concentrations compared to the mothers of the controls. Low haemoglobin during pregnancy is associated with poor neonatal outcomes not limited to preterm births and very low birth weights [28]. However, after the regression analysis, the infants' responses were not affected by their haemoglobin concentrations, as shown in Additional File 2. These findings show an increased risk for these mothers, especially resulting in preterm infants and low birth weight infants.

Strengths and limitations

In this study, infant case samples were matched with controls regarding age and gender to control for confounder biases. We report that the study had some limitations. The number of participants with active TB was limited, resulting in a small sample size for the study. However, we were able to demonstrate a statistically supported difference. Some of our participants were enrolled during the puerperium, so the infants had prior vaccination before enrolment. This limited our understanding of the initial status of these infants before vaccination. Finally, this study did not collect data on maternal tetanus toxoid vaccination during pregnancy; therefore, we cannot conclusively determine its effect on infant baseline titres.

Conclusion

Infants born to mothers with active TB disease: (i) Had low birth weights, (ii) Presented with reduced vaccine-specific IgG responses for BCG and the other infant vaccines in general but markedly at baseline. This could be resulting from persistent *Mycobacterial tuberculosis* antigenemia. We speculate a similar scenario to the Developmental Origins of Health and Disease (*DoHAD)* theory, which suggests that early life exposures can permanently impact health and increase the risk of disease later in life. We propose a larger prospective study with longer follow-ups to explore outcomes of vaccination and TB disease risk. This would also answer whether the suppressed response to the vaccine among exposed infants is due to other factors such as the participant's household or environment and nutrition, in addition to revealing whether the responses improve or completely diminish over time. A study on determining the quality of antibodies from active TB mothers, which would look at antibody affinity and avidity to compare these between cases and controls, is necessary. Finally, looking at the transcriptomic changes in the blood of these infants exposed to TB would be insightful. This would inform some of the highly expressed biomarkers potentially used to diagnose childhood TB.

Abbreviations

TB	Tuberculosis
ATB	Active tuberculosis
BCG	Bacille Calmette-Guérin
DPT	Diphtheria
IgG	Immunoglobulin G
PPD	Purified Protein Derivative
ELISA	Enzyme-Linked Immunosorbent Assay
HIV	Human Immunodeficiency Virus
MD	Mean Difference
IU/mL	International Units per millilitre
g/dL	grams per decilitre
IQR	Interquartile range
CI	Confidence Interval
SE	Standard Error
OD	Optical Density
ANC	Ante-Natal Care

PNC Post-Natal Care
Cat No Catalogue Number

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12865-025-00692-w.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions
DS performed laboratory experiments, analyzed data, and drafted the manuscript. IAB, AN, SC, RN, FB, JBB, PS, APK, DK, RJW, and NR participated in the concept development and reviewed the manuscript. PS developed the experimental protocols that followed the experiment and offered technical laboratory training to perform the experiments. IAB sourced funding for the research.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethical approval
This study received ethical approval from the School of Medicine Research and Ethics Committee (SOMREC reference number SOM 2020-11); the School of Biomedical Sciences (SOBSREC reference number SBS-2022-226) at Makerere University; and the Uganda National Council for Science and Technology (UNCST registration number HS1396ES). The mothers provided written informed consent and assent for their infants to participate in the study.

Competing interests
The authors declare no competing interests.

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