



Bacteria and Bacterial Diseases

Bordetella pertussis infection and antibody dynamics in household cohorts in two South African communities, 2016 – 2018: findings from the PHIRST study

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SUMMARY

Introduction and methods: In a cohort study, enrolling new households annually during 2016–2018, we estimated the *B. pertussis* attack rate using serology and PCR, identified factors associated with seroconversion, and described antibody changes over time. Nasopharyngeal swabs were collected biweekly for 6–10 months annually, with cases defined as individuals testing PCR-positive at least once. Seroconversion was defined as a ≥ 4 -fold increase in anti-pertussis toxin IgG concentration between consecutive blood draws. Logistic regression was used to identify factors associated with seroconversion among PCR-positive individuals.

Results: Among 1509 participants, the serology attack rate was 5.8% (87/1509), 6.2% (94/1509) by PCR, and 9.6% (145/1509) combining both methods. Among PCR-positive cases, 38.3% (36/94) seroconverted, with a mean time to seroconversion of 2.9 months (range: 3 weeks–5.9 months). Younger participants (5–18 years) (adjusted odds ratio (aOR) 6.8, 95% confidence interval (CI) 1.3–35.1) and those with episode durations of ≥ 7 days (aOR 13.3, 95% CI 3.4–51.1) were more likely to seroconvert. Among the seroconverted, 75.0% (27/36) maintained antibody concentrations > 40 IU/ml for at least 12 months post-infection.

Discussion: Almost 10% of participants had *B. pertussis* infection during follow-up. Less than half of individuals with PCR-confirmed infection seroconverted but maintained elevated antibodies for at least one-year post-infection.

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Introduction

Pertussis is a highly infectious respiratory disease caused by *Bordetella pertussis*.¹ Despite widespread use of vaccines globally,

there has been a resurgence of pertussis in recent years in multiple regions, including those with high vaccine coverage.²

Pertussis serology is recommended as a diagnostic tool for older individuals who present with prolonged, undiagnosed respiratory symptoms or during respiratory outbreaks to confirm infection within the population.^{3,4} The most specific serodiagnostic target for pertussis is measuring IgG antibodies against pertussis toxin (PT).² However, the detection of high anti-PT IgG concentrations could be indicative of infection and/or recent vaccination.⁵ Although there are no universally accepted immunological correlates of protection against *B. pertussis* infection,^{1–3} reported data indicate that antibodies against pertactin, fimbriae, and PT may correlate with protection against clinical disease.⁶ Serology can also be a useful tool to understand antibody kinetics and duration of immunity following natural infection or vaccination.¹ Following infection/vaccination, pertussis-specific antibodies increase and then wane in a bi-phasic manner (initial rapid decay from peak followed by slower decay lasting years), and post-infection antibodies decay almost two times faster when compared to post-vaccination antibodies.⁷ Overall, waning generally occurs within 12 months of either natural infection or vaccination.^{7–11}

In 2009, South Africa switched from the whole-cell pertussis vaccine to the acellular vaccine for the primary series administered to infants at 6, 10, and 14 weeks, followed by a booster dose at 18 months, with no further booster doses offered to older individuals.¹² *B. pertussis* surveillance was incorporated in influenza-like illness and pneumonia surveillance programmes in South Africa in 2012 and peaks of infection have been reported in 2015, 2018 and post-COVID-19 pandemic in 2022.^{13–17} We previously reported findings from the Prospective Household cohort study of Influenza, Respiratory Syncytial virus and other respiratory pathogens community burden and Transmission dynamics in South Africa (PHIRST) study, which investigated the incidence and transmission dynamics of *B. pertussis* in two South African communities between 2016 and 2018.¹⁴ In the study, nasopharyngeal swabs were collected twice weekly from household members and tested by PCR. A total of 118 episodes of *B. pertussis* infection were detected in 107 participants, with 11 participants having two episodes of infection. The study highlighted a high incidence of PCR-confirmed *B. pertussis* infection [0.21 (95% CI 0.17 – 0.25)/100 person-weeks], with 68% of infected individuals being colonized.¹⁴ Of the 107 persons positive for *B. pertussis*, only 34 (31.8%) reported symptoms during any given episode of infection. Transmission within households was associated with longer infection duration, and incomplete vaccination among children <5 years of age was associated with increased infection risk. For the current study, we used sera collected from the same cohort to estimate the *B. pertussis* seroprevalence over time, serological infection attack rates, factors associated with infection and seroconversion, and to describe the antibody dynamics of infected individuals over time. These additional analyses complement the PCR-based findings by offering a broader understanding of population immunity and the infection burden in the community. In addition, there are currently no data describing the seroepidemiology of *B. pertussis* in South Africa, and these studies are imperative to quantify the true burden (missed by other laboratory methods) of *B. pertussis* infection.

Materials and methods

Study population

During 2016, 2017 and 2018, the PHIRST study was conducted in two South African communities, one rural (Mpumalanga Province) and one urban (North West Province), annually enrolling consenting members of randomly selected households.¹⁸ A total of 1684

individuals from 327 households were enrolled: 542 individuals in 2016, 577 in 2017, and 565 in 2018, as previously described.¹⁴

Household visits, specimen collection and laboratory testing

Demographic and baseline health status (including HIV) were collected for all participants at enrollment. Vaccination status was obtained for children aged <5 years using their road-to-health vaccination card. During the follow-up period, individuals were visited twice weekly for 6–10 months (starting from January to April to October), which resulted in a total of 105 783 visits during the 3-year study period. During each visit, nasopharyngeal (NP) specimens were collected from participants, and symptom data were documented using a structured questionnaire. Specimens were transported to a centralized laboratory and tested for *B. pertussis* using a duplex real-time PCR detecting IS481 and human *RNaseP* gene (cycle threshold (C_t) < 36 for *RNaseP* is indicative of good sample quality) targets.¹⁴ Any specimen that tested positive for IS481 with C_t values ≤ 45 was repeated (from extraction using a fresh aliquot) and re-tested (two replicates) using a second, multitarget real-time PCR assay targeting *B. pertussis*, *B. parapertussis* and *B. holmesii*.^{14,19} A specimen was considered positive for *B. pertussis* if IS481 and/or *ptxS1* targets were detected with C_t values ≤ 45 in at least 2/3 replicates and negative for *hIS1001* (*B. holmesii*) and *pIS1001* (*B. parapertussis*).^{13,14}

Serum was collected at enrollment, the midpoint and at the end of the follow-up period (± 5 months between serum collections) in 2017 and 2018 cohorts. For the 2016 cohort, serum was only collected at the midpoint and at the end of follow-up (due to study delays). Serum was also collected from the 2016 and 2017 cohorts in subsequent study years (2017 and 2018) (Fig. 1). In total, the 2016, 2017 and 2018 cohorts had 8, 6 and 3 blood draws, respectively. The blood draws were labeled as blood draw 1 to blood draw 8 and corresponded to the following periods of collection: blood draw 1: Mar–Apr 2016; blood draw 2: Oct–Nov 2016; blood draw 3: Feb–Mar 2017; blood draw 4: May 2017; blood draw 5: Oct 2017; blood draw 6: Jan–Feb 2018; blood draw 7: May–Jun 2018; blood draw 8: Oct 2018. For this analysis, only individuals with at least one serum sample collected at any point were included.

Blood specimens were centrifuged at the site within eight hours of collection, and serum was aliquoted and stored at -80°C before being shipped to the National Institute for Communicable Diseases in Johannesburg. Detection of anti-PT IgG was performed using the quantitative anti-PT ELISA kit (EUROIMMUN, Lubeck, Germany)²⁰ that has been calibrated to the WHO International Standard 06/140. Following the kit instructions, in addition to the EUROIMMUN kit controls, an additional positive and negative control was added to each ELISA plate, and each serum specimen was tested once. According to the kit recommendations, IgG anti-PT levels <40, ≥ 40 – <100, and ≥ 100 IU/ml were interpreted as follows: no indication of an acute infection, indeterminate, and indication of acute infection or recent vaccination, respectively.

Data analysis

B. pertussis seroprevalence was calculated for each blood draw (up to eight time points) for individuals that had at least one serum sample collected ($N=1618$) as: total number of individuals with anti-PT IgG concentration ≥ 100 IU/ml /total number of individuals tested $\times 100$.

Seroconversion was calculated for individuals with ≥ 2 consecutive sera collected ($N=1509$) and defined as a ≥ 4 -fold rise in anti-PT IgG concentration^{21–23} between any two consecutive blood draws and/or if anti-PT IgG reached > 100 IU/ml (with or without a 4-fold rise). The attack rate (number of individuals positive/number of individuals tested) by seroconversion and/or PCR (≥ 1 positive swab)

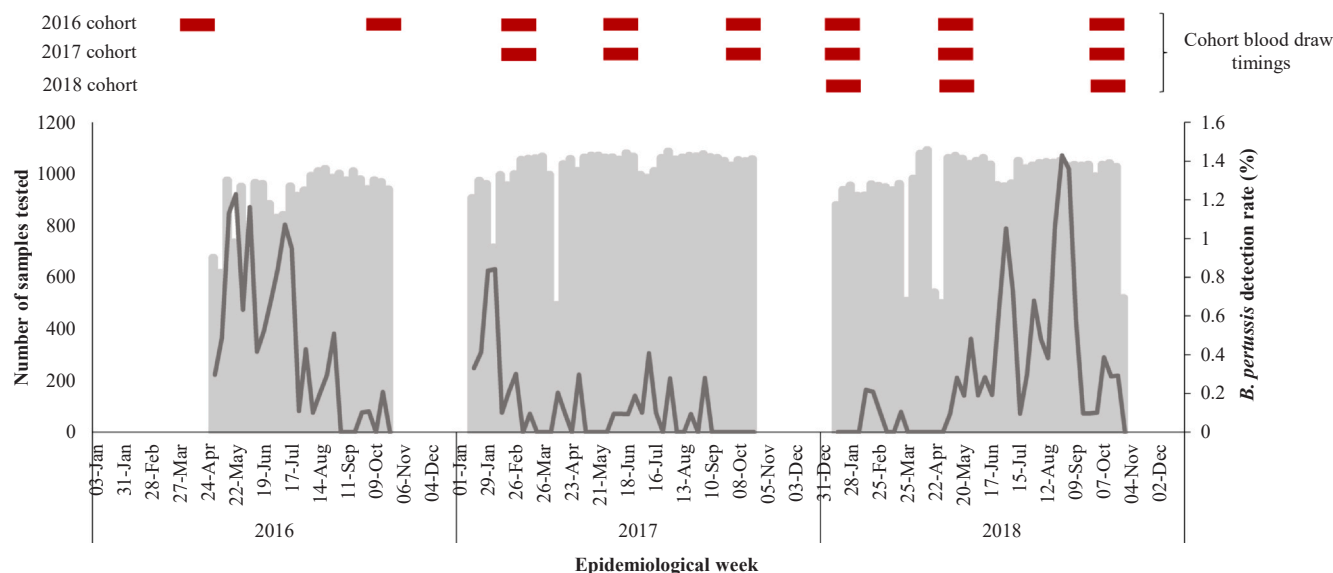


Fig. 1. Number of nasopharyngeal specimens collected and tested for *B. pertussis* by PCR per week (gray bars), percent testing PCR positive (black line) and timing of blood collection (blood draws 1 – 8, red blocks) for the PHIRST study cohort, South Africa, 2016–2018. Note: 2016 cohort = 8 blood draws; 2017 cohort = 6 blood draws; 2018 cohort = 3 blood draws. Blood draw 1: Mar–Apr 2016; blood draw 2: Oct–Nov 2016; blood draw 3: Feb–Mar 2017; blood draw 4: May 2017; blood draw 5: Oct 2017; blood draw 6: Jan–Feb 2018; blood draw 7: May–Jun 2018; blood draw 8: Oct 2018.

during the follow-up period was calculated and compared using a chi-squared test. We also performed a sensitivity analysis by comparing attack rates defined as a ≥ 2 -fold rise in anti-PT IgG concentration as seroconversion to a ≥ 4 -fold rise.

To determine factors associated with seroconversion among individuals with PCR-confirmed infection, we used logistic regression analysis, accounting for clustering by site and household using a hierarchical mixed effects model. Individual factors assessed included: sex, age group, HIV serostatus, nutritional status, underlying medical conditions, pertussis vaccination (for children < 5 years), episode duration [defined as date of the last PCR-positive specimen minus the date of the first PCR-positive specimen (within the same episode of infection) plus 2.5 days to account for gaps between visits¹⁴], household size, household crowding (defined as > 2 persons in a household sleeping in the same room) and presence of a child aged < 5 years living in the household. Factors associated with *B. pertussis* infection (identified by PCR and/or serology) were also determined using hierarchical mixed effects logistic regression. For the multivariable models, we assessed all variables that were significant at $p < 0.2$ on univariate analysis, and removed non-significant factors ($p \geq 0.05$) with manual backward stepwise elimination. Statistical significance was determined at $p < 0.05$.

To describe changes in antibody concentrations over time for individuals with PCR-confirmed infection that seroconverted (visit date of first PCR-positive specimen considered as day 0 of infection), we described the number of individuals that seroconverted and the time taken (in months) for anti-PT IgG concentrations to reach a ≥ 4 -fold rise and to decrease to below 40 IU/ml. We described antibody dynamics in individuals who were likely to have received the acellular vaccine in the routine infant immunization schedule (born in 2009 or later) and those who were likely to have received the whole cell vaccine (born before 2008). This assumption was made based on the vaccine received according to the individual's date of birth, as vaccination history was only documented for children under 5 years old. Individuals born in 2008 were excluded from these analyses as they could have received either vaccine.

Data analyses were performed using Stata version 14.1 (Stata Corp LP, College Station, Texas, USA), GraphPad Prism version 10.2 (Dotmatics, Boston, USA) and Microsoft Excel (Microsoft Inc., Washington, USA).

Ethics

Ethical approval for the PHIRST study was obtained from the University of the Witwatersrand Human Research Ethics Committee, South Africa [(protocol number: 150808) - see 45 C.F.R. part 46.114; 21 C.F.R. part 56.114.]. A separate ethics application for the pertussis component of the PHIRST project was obtained from the University of the Witwatersrand Human Research Ethics Committee, South Africa (protocol number: M210676).

Results

Study population

From 2016 through 2018, 1684 individuals were enrolled in the PHIRST study. Of these, 96.1% (1618/1684) had at least one serum sample collected, and 89.6% (1509/1684) had ≥ 2 serum samples collected. Serum from 66 individuals was not tested due to insufficient volume. Of those with at least one serum sample collected, 13.8% (223/1618) were aged < 5 years, 15.9% (249/1570) were living with HIV, and 97.8% (175/179) of these were fully vaccinated for age, with the acellular vaccine (of those with available vaccine status) (Table 1). A total of 105 687 NP swabs were collected, with 276 (0.3%) testing PCR-positive for *B. pertussis* (Fig. 1). In addition, 413 (0.4%) swabs were PCR-positive for *B. holmesii*; however, *B. parapertussis* was not detected.

B. pertussis seroprevalence over time

A total of 7170 serum samples were collected from 1618 (96.1%) individuals. Seroprevalence (anti-PT IgG ≥ 100 IU/ml) was 3.9% (13/332) at the start of the study in March/April 2016, peaking at 5.2% (71/1363) in October 2018 (blood draw 8) (Fig. 2). The lowest seroprevalence (1.6%, 23/1419) was observed from January to February 2018 (blood draw 6).

The majority of individuals across all age groups maintained anti-PT IgG concentrations below 40 IU/ml, with only a small percentage of individuals having antibody concentrations exceeding 100 IU/ml (Fig. 3). Compared to other age groups, a higher proportion of individuals aged 5–18 years (Fig. 3b.) had elevated anti-PT IgG

Table 1

Demographic, clinical and household characteristics of individuals (≥ 1 serum collected) enrolled into the PHIRST study and tested by anti-PT IgG ELISA, South Africa, 2016 – 2018 (N=1618).

Characteristic	Overall n/N (%)	Rural n/N (%)	Urban n/N (%)
Year			
2016	529/1618 (32.7)	271/812 (33.4)	258/806 (32.0)
2017	553/1618 (34.2)	275/812 (33.9)	278/806 (34.5)
2018	536/1618 (33.1)	266/812 (32.8)	270/806 (33.5)
Sex			
Male	644/1618 (39.8)	298/812 (36.7)	346/806 (42.9)
Female	974/1618 (60.2)	514/812 (63.3)	460/806 (57.1)
Age group (years)			
< 1	17/1618 (1.1)	8/812 (1.0)	9/806 (1.1)
1–4	206/1618 (12.7)	132/812 (16.3)	74/806 (9.2)
5–14	540/1618 (33.4)	303/812 (37.3)	237/806 (29.4)
15–24	271/1618 (16.8)	124/812 (15.2)	147/806 (18.2)
25–44	316/1618 (19.5)	141/812 (17.4)	175/806 (21.7)
45–64	195/1618 (12.1)	74/812 (9.1)	121/806 (15.0)
≥ 65	73/1618 (4.5)	30/812 (3.7)	43/806 (5.3)
HIV status			
Negative	1321/1570 (84.1)	683/800 (85.4)	638/770 (82.9)
Positive	249/1570 (15.9)	117/800 (14.6)	132/770 (17.1)
Nutritional status^a			
Underweight	127/1611 (7.9)	54/812 (6.7)	73/799 (9.1)
Normal	937/1611 (58.2)	518/812 (63.8)	419/799 (52.4)
Overweight	263/1611 (16.3)	122/812 (15.0)	141/799 (17.7)
Obese	284/1611 (17.6)	11/812 (14.5)	166/799 (20.8)
Underlying illness^b			
No	1572/1618 (97.2)	808/812 (99.5)	764/806 (94.8)
Yes	46/1618 (2.8)	4/812 (8.7)	42/806 (5.2)
Pertussis vaccination^c (for age)			
Incomplete vaccination	4/179 (2.2)	2/107 (1.9)	2/72 (2.8)
Fully vaccinated	175/179 (97.8)	105/107 (98.1)	70/72 (97.2)
Number of household members			
≤ 5	768/1618 (47.5)	362/812 (44.5)	406/806 (50.3)
6–10	728/1618 (45.0)	385/812 (47.4)	343/806 (42.6)
> 10	122/1618 (7.5)	65/812 (8.0)	57/806 (7.1)
Children < 5 years in household			
No	466/1618 (28.8)	90/812 (11.1)	376/806 (46.7)
Yes	1152/1618 (71.2)	722/812 (88.9)	430/806 (53.4)
Crowding^d			
No	712/1618 (44.0)	90/812 (11.1)	376/806 (46.7)
Yes	906/1618 (56.0)	722/812 (88.9)	430/806 (53.4)

^a Nutritional status based on individual's body mass index (BMI).

^b Underlying illness was defined as self-reported history of asthma, lung disease, heart disease, stroke, spinal cord injury, epilepsy, organ transplant, immunosuppressive therapy, organ transplantation, cancer, liver disease, renal disease or diabetes.

^c Only collected for children < 5 years of age.

^d Crowding was defined as more than two individuals in a household sleeping in the same room.

concentrations, whereas those aged < 5 years (Fig. 3a) and ≥ 19 years (Fig. 3c) showed lower anti-PT IgG concentrations.

B. pertussis attack rates by PCR and serology

Comparing PCR with serology for the identification of *B. pertussis* infection, the attack rate was similar using both methodologies, [PCR (6.2%, 94/1509) vs. serology (5.8%, 87/1509); $p=0.64$] (Table 2). Over the study period, thirty-six individuals (2.4%, 36/1509) tested positive by both methods and 145 (9.6%, 145/1509) individuals were identified as infected using either PCR or seroconversion.

Comparison of a ≥ 2 -fold rise and ≥ 4 -fold rise in anti-PT IgG antibodies

Using a ≥ 2 -fold rise in antibody concentration to define infection, the serology-determined attack rate was 8.5% (128/1509), compared to 5.8% (87/1509) with a ≥ 4 -fold rise ($p=0.04$). However, when correlated with PCR-confirmed cases, there was no difference in the number of PCR-positive cases with seroconversion (only one additional case detected) between the ≥ 2 -fold rise (2.5%, 37/1509) and ≥ 4 -fold rise (2.4%, 36/1509), $p=0.91$.

Individuals positive for *B. pertussis* by PCR with no seroconversion

Of the 58 individuals with PCR-confirmed infection with no evidence of seroconversion, 74.1% (43/58) had an episode duration of < 7 days, while 25.9% (15/58) had an episode duration of ≥ 7 days (Supplementary Figure 1). Among the 15 cases with longer PCR-episode durations who did not seroconvert, two cases from the 2018 cohort, only tested PCR-positive at the end of the follow-up and therefore had no serum collected after the PCR-confirmed infection. The remaining 13 individuals (86.7%, 13/15) had serum collected 1.1–5.9 months after testing PCR positive. Eight of the individuals with longer PCR-episode durations (53.3%, 8/15) that had serum collected 1.1–5.9 months after testing PCR positive were from two households that had family members who were positive by both PCR and serology during the same time period. All eight individuals had IS481 C_t values > 35 and episode duration of < 7 days. Among individuals only PCR-positive ($n=58$), the mean ($\pm$ standard deviation) PCR-episode duration was 11.3 days (± 20.8); however, for cases PCR-positive with seroconversion ($n=36$), the mean episode duration was 18.8 days (± 20.2), ($p=0.09$).

Individuals positive for *B. pertussis* by serology only

Twelve PCR-negative individuals (13.8%, 12/87) showed seroconversion during the follow-up period. Of these, eight (66.7%, 8/

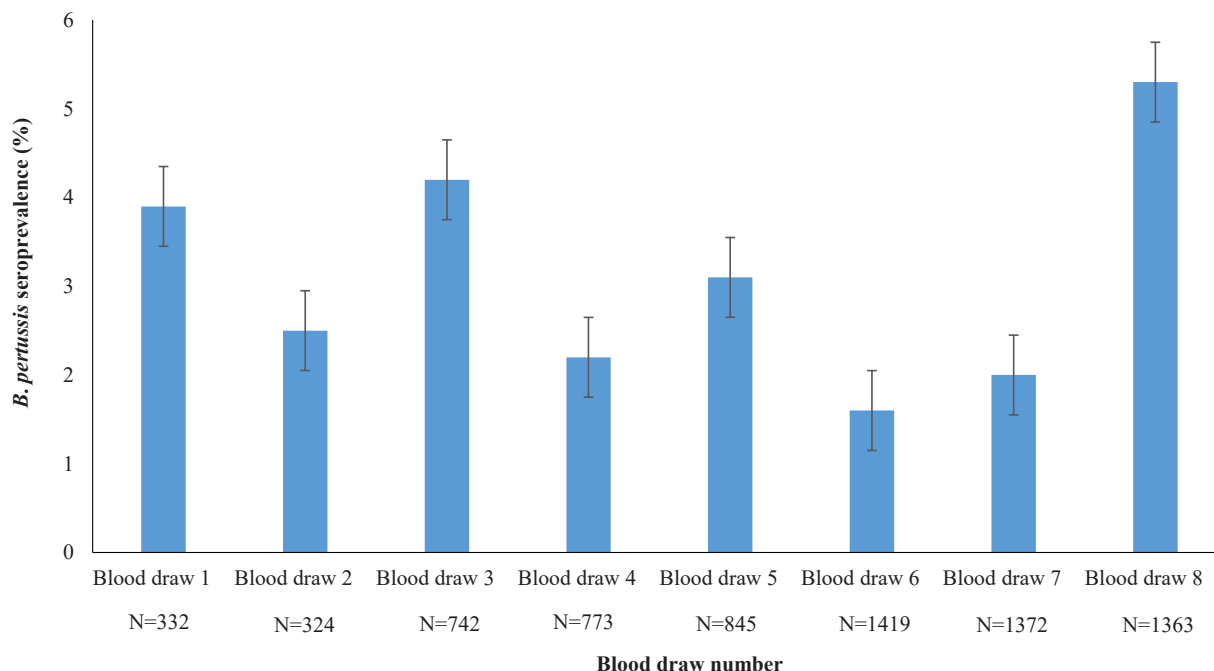


Fig. 2. Seroprevalence of *B. pertussis* over the study period (per blood draw), PHIRST study, South Africa, 2016 – 2018. (Blood draw 1: Mar – Apr 16; Blood draw 2: Oct – Nov 16; Blood draw 3: Feb – Mar 17; Blood draw 4: May 17; Blood draw 5: Oct 17; Blood draw 6: Jan – Feb 18; Blood draw 7: May – Jun 18; Blood draw 8: Oct 18). Error bars represent the 95% confidence interval.

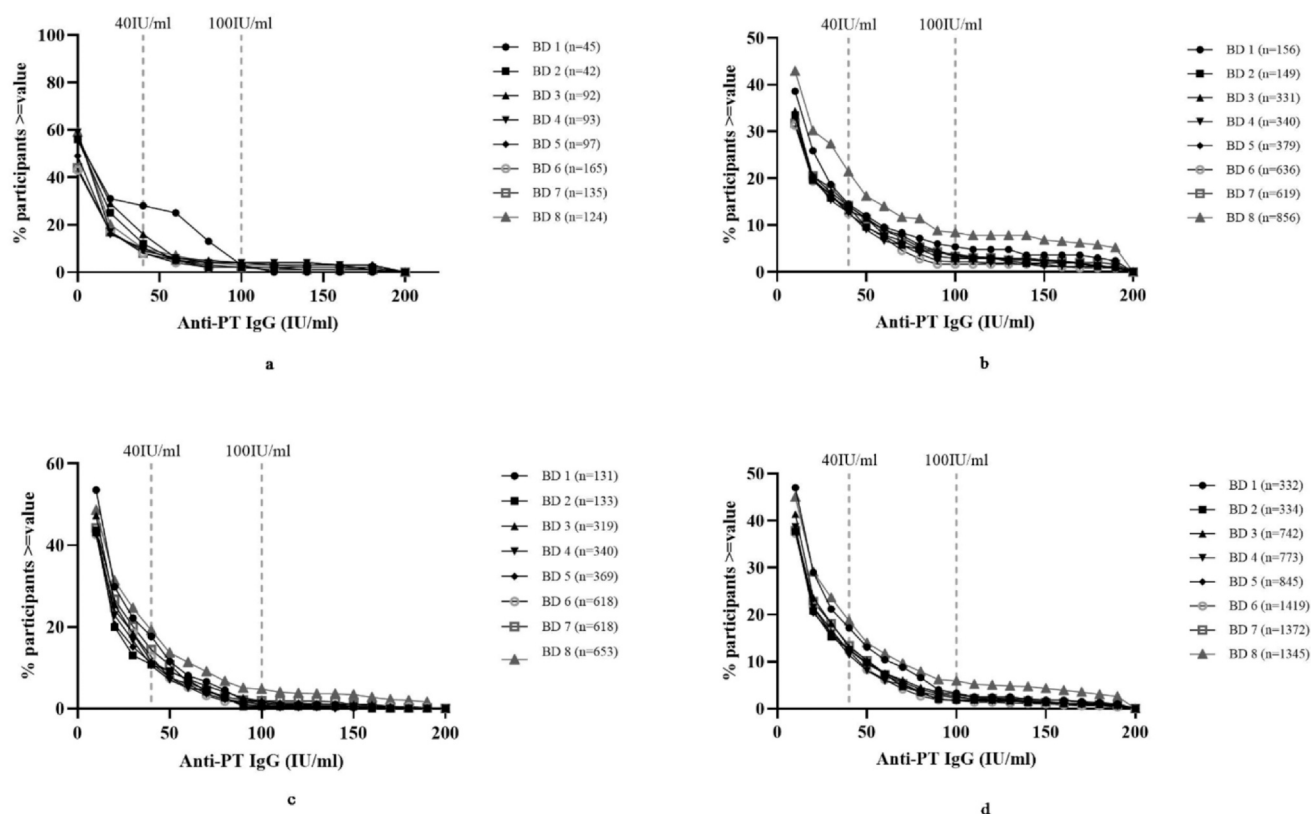


Fig. 3. Reverse cumulative distribution plots of anti-pertussis toxin (PT) IgG concentrations stratified by age group: (a) <5 years, (b) 5–18 years, (c) ≥19 years, and (d) all age groups and blood draw (BD), PHIRST study, South Africa, 2016 – 2018. (Blood draw 1: Mar – Apr 16; Blood draw 2: Oct – Nov 16; Blood draw 3: Feb – Mar 17; Blood draw 4: May 17; Blood draw 5: Oct 17; Blood draw 6: Jan – Feb 18; Blood draw 7: May – Jun 18; Blood draw 8: Oct 18).

Table 2*B. pertussis* attack rate by PCR, serology and a combination of both methods, PHIRST study, South Africa, 2016 – 2018 (N=1509).

Characteristic	Individuals positive by PCR n/N (%)	Individuals positive by serology n/N (%)	Individuals positive by both PCR and serology n/N (%)	Individuals positive by PCR and/or serology n/N (%)
Attack rate	94/1509 (6.2)	87/1509 (5.8)	36/1509 (2.4)	145/1509 (9.6)
Year				
2016	26/507 (5.1)	38/507 (7.5)	8/507 (1.6)	56/507 (11.1)
2017	23/518 (4.4)	23/518 (4.4)	9/518 (1.7)	37/518 (7.1)
2018	45/484 (9.3)	26/484 (5.4)	19/484 (3.9)	52/484 (10.7)
Gender				
Male	41/600 (6.8)	34/600 (5.7)	15/600 (2.5)	60/600 (10.0)
Female	53/909 (5.8)	53/909 (5.8)	21/909 (2.3)	85/909 (9.4)
Age group (years)				
< 5	7/181 (3.9)	8/181 (4.4)	2/181 (1.1)	13/181 (7.2)
5–18	56/670 (8.4)	46/670 (6.9)	25/670 (3.7)	77/670 (11.5)
19–44	18/389 (4.6)	17/389 (4.4)	4/389 (1.0)	31/389 (7.9)
≥45	13/259 (5.0)	15/259 (5.8)	5/259 (1.9)	23/259 (8.9)
HIV status				
Negative	81/1238 (6.5)	76/1238 (6.1)	33/1238 (2.7)	124/1238 (10.0)
Positive	12/230 (5.2)	11/230 (4.8)	3/230 (1.3)	20/230 (8.7)
Nutritional status^a				
Underweight	8/119 (6.7)	6/119 (5.0)	1/119 (0.8)	13/119 (10.9)
Normal	58/874 (6.6)	52/874 (5.9)	24/874 (2.8)	86/874 (9.8)
Overweight	14/244 (5.7)	10/244 (4.1)	4/244 (1.6)	20/244 (8.2)
Obese	13/270 (4.8)	19/270 (7.0)	7/270 (2.6)	25/270 (9.3)
Underlying illness^b				
No	89/1464 (6.1)	83/1464 (5.7)	34/1464 (2.3)	138/1464 (9.4)
Yes	5/45 (11.1)	4/45 (8.9)	2/45 (4.4)	7/45 (15.6)
Pertussis vaccination^c				
Unvaccinated	1/4 (25.0)	0/4 (0.0)	0/4 (0.0)	1/4 (25.0)
At least 1 dose	5/138 (3.6)	6/138 (4.4)	2/138 (1.4)	9/138 (6.5)
IS481 C_t (mean)				
< 34	20/20 (100.0)	N/A	15/20 (75.0)	20/20 (100.0)
34–39	54/54 (100)	N/A	16/54 (29.6)	54/54 (100)
40–45	20/20 (100.0)	N/A	5/20 (25.0)	20/20 (100.0)
PCR episode duration				
< 7 days	55/55 (100.0)	N/A	11/55 (20.0)	55/55 (100.0)
≥7 days	39/39 (100.0)	N/A	25/39 (64.10)	39/39 (100.0)
Number of household members				
≤5	35/714 (4.9)	36/714 (5.0)	12/714 (1.7)	59/714 (8.3)
6–10	50/679 (7.4)	40/679 (5.9)	17/679 (2.5)	73/679 (10.8)
> 10	9/116 (7.8)	11/116 (9.5)	7/116 (6.0)	13/116 (11.2)
Children < 5 years in household				
No	28/437 (6.4)	26/437 (5.9)	7/437 (1.6)	47/437 (10.8)
Yes	66/1072 (6.2)	61/1072 (6.7)	29/1072 (2.7)	98/1072 (9.1)
Crowding^d				
No	32/664 (4.8)	34/664 (5.1)	10/664 (1.5)	56/664 (8.4)
Yes	62/845 (7.3)	53/845 (6.3)	26/845 (3.1)	89/845 (10.5)

The *B. pertussis* attack rate was calculated as follows: no. individuals positive / no. individuals tested using serology (seroconversion between any 2 consecutive blood draws) and/or PCR (≥1 positive swab).

^a Nutritional status based on individual's body mass index (BMI).

^b Underlying illness defined as self-reported history of asthma, lung disease, heart disease, stroke, spinal cord injury, epilepsy, organ transplant, immunosuppressive therapy, organ transplantation, cancer, liver disease, renal disease or diabetes.

^c Only collected for children < 5 years of age.

^d Crowding - more than two individuals in a household sleeping in the same room. NA - not applicable. C_t - cycle threshold.

12) were children under 10 years old, and all were HIV-negative. In addition, all NP swabs (for PCR) collected from these individuals during the follow-up period had *RNase P* (sample quality) C_t values of < 33, indicating good quality specimens.

Factors associated with seroconversion in individuals PCR-positive for *B. pertussis*

On multivariable analysis, PCR-positive individuals aged 5–18 years were more likely to seroconvert compared to those aged 19–44 years (adjusted odds ratio (aOR) 6.84, 95% confidence interval (CI) 1.33–35.08) (Table 3). Additionally, individuals with an episode duration of ≥7 days were more likely to seroconvert than those with episodes < 7 days (aOR 13.31, 95% CI 3.43–51.49). On univariate analysis individuals PCR-positive for *B. pertussis*

with IS481 C_t values < 34 were 11.7 times more likely to seroconvert than those with C_t values of 40–44 (OR 11.72, 95% CI 2.15–64.0), however, on multivariable analysis, this result was not significant.

Factors associated with *B. pertussis* infection – individuals positive for *B. pertussis* by either PCR and/or serology

Exploring infection detected by either PCR or serology, using univariate logistic regression analysis, individuals aged 5–18 years were at an increased risk of *B. pertussis* infection [OR 1.67 (95% CI 1.00 – 2.78)] compared to those aged 19–45 years. However, due to small numbers we were underpowered for the multivariable model (Table 4).

Table 3Proportion of individuals PCR-positive for *B. pertussis* that seroconverted against anti-PT IgG and factors associated with seroconversion, PHIRST study, South Africa, 2016 – 2018 (N=94).

Characteristic	<i>B. pertussis</i> PCR cases with seroconversion n/N (%)	Univariate analysis		Multivariable analysis	
		Odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value
Overall	36/94 (38.3)	–	–	–	–
Sex					
Male	15/41 (36.6)	Reference			
Female	21/53 (39.6)	1.10 (0.35 – 3.42)	0.86		
Age group (years)					
< 5	2/7 (28.6)	1.98 (0.15 – 25.66)	0.60	3.01 (0.22 – 41.06)	0.41
5–18	25/56 (44.6)	4.25 (0.86 – 21.13)	0.07	6.84 (1.33 – 35.08)	0.02
19–44	4/18 (22.2)	Reference		Reference	
≥45	5/13 (38.5)	4.59 (0.53 – 39.91)	0.17	6.13 (0.74 – 50.45)	0.09
HIV status					
Uninfected	33/81 (40.7)	Reference			
Infected	3/12 (25.0)	0.29 (0.04 – 1.85)	0.19		
Nutritional status^a					
Underweight	1/8 (12.5)	0.17 (0.01 – 2.40)	0.19		
Normal	24/58 (41.4)	Reference			
Overweight	4/14 (28.6)	0.40 (0.07 – 2.16)	0.29		
Obese	7/13 (5.9)	1.52 (0.32 – 7.28)	0.59		
Underlying illness^b					
No	34/89 (38.2)	Reference			
Yes	2/5 (40.0)	0.96 (0.09 – 9.69)	0.97		
Pertussis vaccination^c					
No doses	0/1 (0.0)	Reference			
At least 1 dose	2/5 (40.0)	2.14 (0.05 – 77.53)	0.67		
IS481 C_t (mean)					
< 34	15/20 (75.0)	11.72 (2.15 – 64.0)	0.04		
34–39	16/54 (29.6)	1.53 (0.39 – 5.97)	0.53		
40–45	5/20 (25.0)	Reference			
PCR episode duration					
< 7 days	11/55 (20.0)	Reference		Reference	
≥7 days	25/39 (64.1)	8.95 (2.79 – 28.73)	< 0.001	13.31 (3.43 – 51.49)	
Number of household members					
≤5	12/35 (34.3)	Reference			
6–10	17/50 (34.0)	0.95 (0.29 – 3.10)	0.93		
> 10	7/9 (77.8)	11.01 (0.76 – 158.44)	0.07		
Children < 5 years in household					
No	7/28 (25.0)	Reference			
Yes	29/66 (43.9)	2.06 (0.54 – 7.94)	0.29		
Crowding^d					
No	10/32 (31.3)	Reference			
Yes	26/62 (41.9)	1.74 (0.47 – 6.40)	0.40		

^a Nutritional status based on individual's body mass index (BMI).^b Underlying illness defined as self-reported history of asthma, lung disease, heart disease, stroke, spinal cord injury, epilepsy, organ transplant, immunosuppressive therapy, organ transplantation, cancer, liver disease, renal disease or diabetes.^c Only collected for children < 5 years of age. Vaccine status calculated based on number of doses of vaccine received by age.^d Crowding - more than two individuals in a household sleeping in the same room. Bold font indicates statistical significance. C_t - cycle threshold. Variables adjusted for in final model: Age group and PCR episode duration.

B. pertussis anti-PT IgG antibody concentrations over time

PCR-negative individuals with no evidence of seroconversion showed varying levels of anti-PT IgG, all below 100 IU/ml (Supplementary Figure 2).

Among the 36 PCR-positive individuals with seroconversion, a ≥4-fold rise in antibody concentration was detected in all cases at the blood draw after the PCR-confirmed infection (Fig. 4). For these individuals, the mean time to serum collection after the first PCR-positive result was 2.9 months (range: 3 weeks to 5.9 months). Following seroconversion (first serum specimen collected following positive PCR result), 61.1% (23/36) had antibody concentrations > 100 IU/ml, while 38.9% (14/36) had concentrations ≥40–< 100 IU/ml. Nineteen of these individuals were excluded from further analysis as seroconversion was detected at the final blood draw. Thirteen individuals (76.5%, 13/17) had concentrations ≥40–< 100 IU/ml 12 months after testing PCR-positive, while the remaining four individuals had concentrations < 40 IU/ml at this time point. Of 11 individuals with two episodes of infection, only two (18.2%) had

seroconversion with anti-PT IgG concentrations ≥40–< 100 IU/ml after the second episode of infection.

Among *B. pertussis* cases (detected by PCR and serology) presumed to have received the whole-cell vaccine [mean age of these individuals (± standard deviation): 31 ± 25 years], 65.0% (13/20) had concentrations > 100 IU/ml post-PCR following seroconversion (blood draw after the PCR-confirmed infection), with 30.8% (4/13) maintaining antibodies > 40 IU/ml 12 months post-PCR positivity (Fig. 5(a)). In those presumed to have received the acellular vaccine [mean age of these individuals (± SD): 6 ± 2 years], 40.0% (4/10) had concentrations > 100 IU/ml, but these antibodies waned to < 40 IU/ml within 12 months post testing PCR positive (Fig. 5(b)).

Discussion

Over three years (2016–2018) in two South African communities, *B. pertussis* seroprevalence ranged from 1.8% to 5.3%, and was highest in the 5–18 years age group. The serology-based attack rate was 5.8%,

Table 4Factors associated with *B. pertussis* infection (individuals positive on serology and/or PCR), PHIRST study, South Africa, 2016 – 2018 (N=1509).

Characteristic	<i>B. pertussis</i> attack rate n/N (%)	Univariate analysis ^a	
		Odds ratio (95% CI)	p-value
Overall	145/1509 (9.6)		
Sex			
Male	60/600 (10.0)	Reference	
Female	85/909 (9.4)	0.92 (0.61 – 1.38)	0.69
Age group (years)			
< 5	13/181 (7.2)	1.11 (0.51 – 2.40)	0.78
5–18	77/670 (11.5)	1.67 (1.00 – 2.78)	0.04
19–44	31/389 (7.9)	Reference	
≥45	23/259 (8.9)	1.23 (0.63 – 2.37)	0.53
HIV status			
Uninfected	124/1238 (10.0)	Reference	
Infected	20/230 (8.7)	0.81 (0.46 – 1.45)	0.49
Nutritional status^b			
Underweight	13/119 (10.9)	1.13 (0.54 – 2.39)	0.73
Normal	86/874 (9.8)	Reference	
Overweight	20/244 (8.2)	0.67 (0.36 – 1.23)	0.19
Obese	25/270 (9.3)	0.91 (0.53 – 1.57)	0.73
Underlying illness^c			
No	138/1464 (9.4)	Reference	
Yes	7/45 (15.6)	1.40 (0.48 – 4.06)	0.53
Pertussis vaccination^d			
Unvaccinated	1/4 (25.0)	5.84 (0.77 – 44.17)	0.09
At least 1 dose	9/138 (6.5)	Reference	
Number of household members			
≤5	59/714 (8.3)	Reference	
6–10	73/679 (10.8)	1.35 (0.77 – 2.38)	0.28
> 10	13/116 (11.2)	1.26 (0.36 – 4.33)	0.71
Children < 5 years in household			
No	47/437 (10.8)	Reference	
Yes	98/1072 (9.1)	0.78 (0.43 – 1.40)	0.41
Crowding^e			
No	56/664 (8.4)	Reference	
Yes	89/845 (10.5)	1.19 (0.69 – 2.06)	0.51

^a Due to small numbers, we were underpowered for the multivariable model.^b Nutritional status based on individual's body mass index (BMI).^c Underlying illness defined as self-reported history of asthma, lung disease, heart disease, stroke, spinal cord injury, epilepsy, organ transplant, immunosuppressive therapy, organ transplantation, cancer, liver disease, renal disease or diabetes.^d Only collected for children < 5 years of age. Vaccine status calculated based on number of doses of vaccine received by age.^e Crowding - more than two individuals in a household sleeping in the same room.

closely matching the PCR attack rate of 6.2%, and the combined attack rate was 9.8%. Among PCR-confirmed cases, 38.3% seroconverted, with a higher likelihood of seroconversion in individuals aged 5–18 years and those with longer episode duration. Seroconversion amongst individuals, defined as a ≥4-fold rise in anti-PT IgG, was typically detected within three months post-infection, and 76.5% maintained antibody levels above 40 IU/ml for up to a year.

This study's strength lies in its intense follow-up of all participants, with repeated sampling regardless of symptoms, enabling the inclusion of asymptomatic cases that may contribute to household transmission. This systematic approach minimized sampling bias, providing robust data to track *B. pertussis* infection and antibody dynamics over time, and amongst PCR-confirmed cases.

In the two communities, *B. pertussis* seroprevalence ranged from 3.9% in 2016 to 1.8% in 2017, then increased to 5.3% by October 2018. These serological findings align with the rise in *B. pertussis* cases reported in South Africa in 2018, as detected through the Notifiable Medical Conditions System, sentinel surveillance for severe respiratory illness, and PCR data from the PHIRST cohort.^{13–15,24} Overall, seroprevalence data vary by region as study

design and study populations differ. A Tunisian seroprevalence study in 2018 amongst asymptomatic adolescents and adults reported a 14% *B. pertussis* seroprevalence.²⁵ Similarly, a Madagascan study conducted amongst children and adolescents reported a seroprevalence of 9.0%.²⁶

Some studies have shown that the detection rate of *B. pertussis* is higher using serology compared to PCR.^{27,28} However, our study found similar attack rates using both methods, indicating that excluding either PCR or serology in our setting may have led to an underestimation of attack rates.

Overall, individuals aged 5–18 years had the highest attack rate, suggesting greater infection risk in this group. This is similar to a 2018 Tunisian study, which reported the highest serological infection rate in older children (13–18 years, 3.1%), compared to younger children aged 6–12 years (1.6%).²⁵ A 2015 Belgian study, in a population using the acellular pertussis vaccine, found that children aged 10–14 years had the highest *B. pertussis* detection rates, compared to other age groups.²⁷ These findings support the WHO's recommendation that older children and adolescents are key sources of *B. pertussis* transmission to unvaccinated infants.² In 2024, South Africa updated its immunization program to include acellular vaccine boosters for children aged six and 12 years and

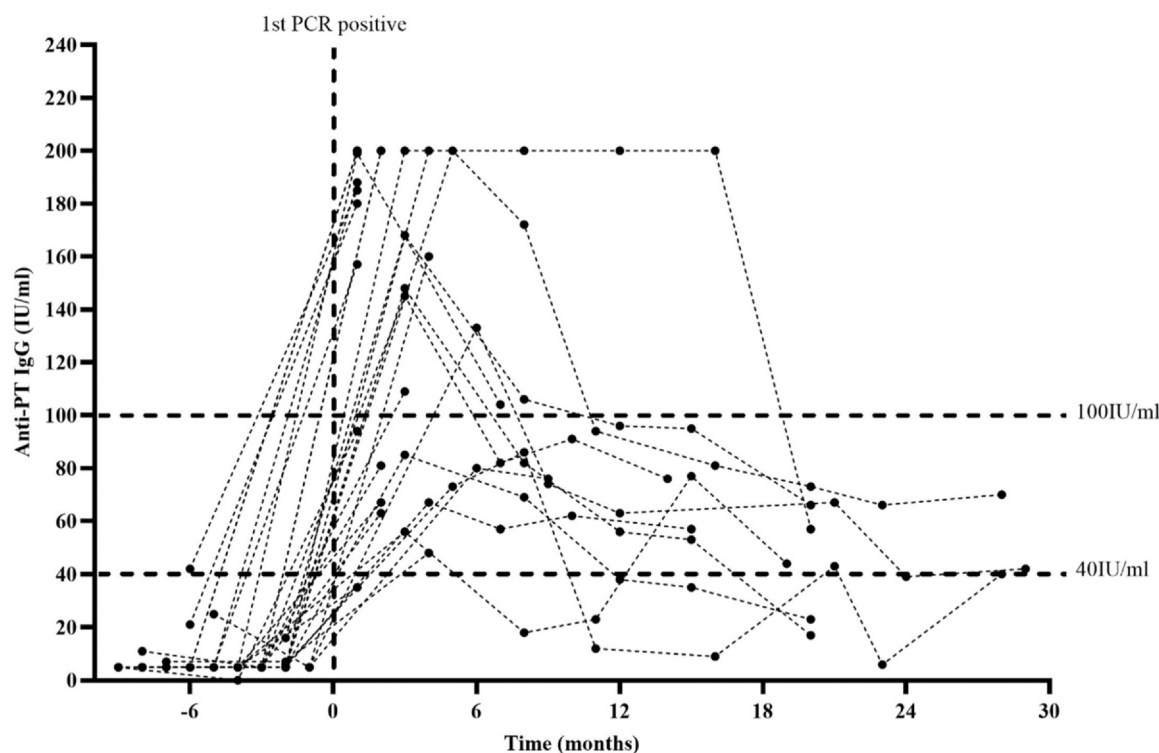


Fig. 4. Anti-PT IgG antibody concentrations in individuals PCR-positive for *B. pertussis* PHIRST study, South Africa, 2016 – 2018.

introduced maternal immunization during every pregnancy, aiming to reduce community transmission and protect at-risk infants.

In our previously published *B. pertussis* data from the PHIRST study, we highlighted that 68% of individuals with PCR-confirmed infection and 39% of index cases within households were asymptomatic.¹⁴ In the current analysis, we incorporated serological data from the same cohort and found that approximately 10% of participants tested positive for *B. pertussis* by PCR during the follow-up period. However, fewer than half of these PCR-positive individuals seroconverted to anti-PT IgG. This limited seroconversion may reflect the high proportion of asymptomatic infections, which could be associated with weaker or absent antibody responses. A longitudinal study conducted in Zambia between 2015–2019, which focused on PCR-confirmed *B. pertussis* infection, reported a high prevalence of asymptomatic cases among mothers and young infants.²⁹ These findings suggest that asymptomatic or mild pertussis infection is common and likely plays an important role in transmission of infection, particularly in household and community settings.

Following infection/vaccination, pertussis-specific antibodies increase and then wane in a bi-phasic manner.⁷ Overall, waning generally occurs within 12 months of either natural infection or vaccination.^{7–11} Amongst our *B. pertussis* cases, we were able to show that anti-PT IgG antibodies following infection, peak within three months and remain elevated for at least a year. Despite differences in study design and serum collection timing, our findings were comparable to other studies. Serum from 11 German adults with pertussis showed an 11-fold increase in antibodies within two months of infection, followed by a rapid decline. However, elevated antibodies (> 40 IU/ml) remained detectable at the 24-month follow-up

visit, with average antibody levels decreasing over time.³⁰ A Danish study found that antibodies in individuals with natural infection or booster vaccination peaked above 75 IU/ml within 17 days of symptom onset, but declined within five months after infection and three months after vaccination.⁷

Our study has limitations that need to be considered. Serum was not collected at optimal or consistent time points relative to *B. pertussis* infection, likely leading to an underestimation of cases with seroconversion and our inability to detect acute infections (individuals presenting with episode durations of <7 days). Ideally, blood samples should be collected 3–6 weeks post-infection and at regular intervals thereafter. We assessed seroconversion only to *B. pertussis* toxin, potentially missing other antigenic responses and further underestimating cases. Due to limited available data, we defined seroconversion as a ≥ 4 -fold rise in anti-PT IgG, which may have led to underestimating cases; however, using a ≥ 2 -fold rise only identified one additional PCR-positive case, so we maintained the more specific 4-fold criterion. We only had vaccine data for children under 5 years of age, and used birth date as a proxy for vaccine type when assessing antibody dynamics in older age groups. Additionally, the small number of pertussis cases limited the statistical power of some analyses.

Within the PHIRST study, there was an overall low seroprevalence of *B. pertussis*. Overall, older children and those with longer infection durations were more likely to seroconvert. The data further highlight that not all individuals (symptomatic and asymptomatic) seroconvert. However, among those who did, antibody levels declined more rapidly in those assumed to have been vaccinated with the acellular vaccine compared to the whole cell vaccine.

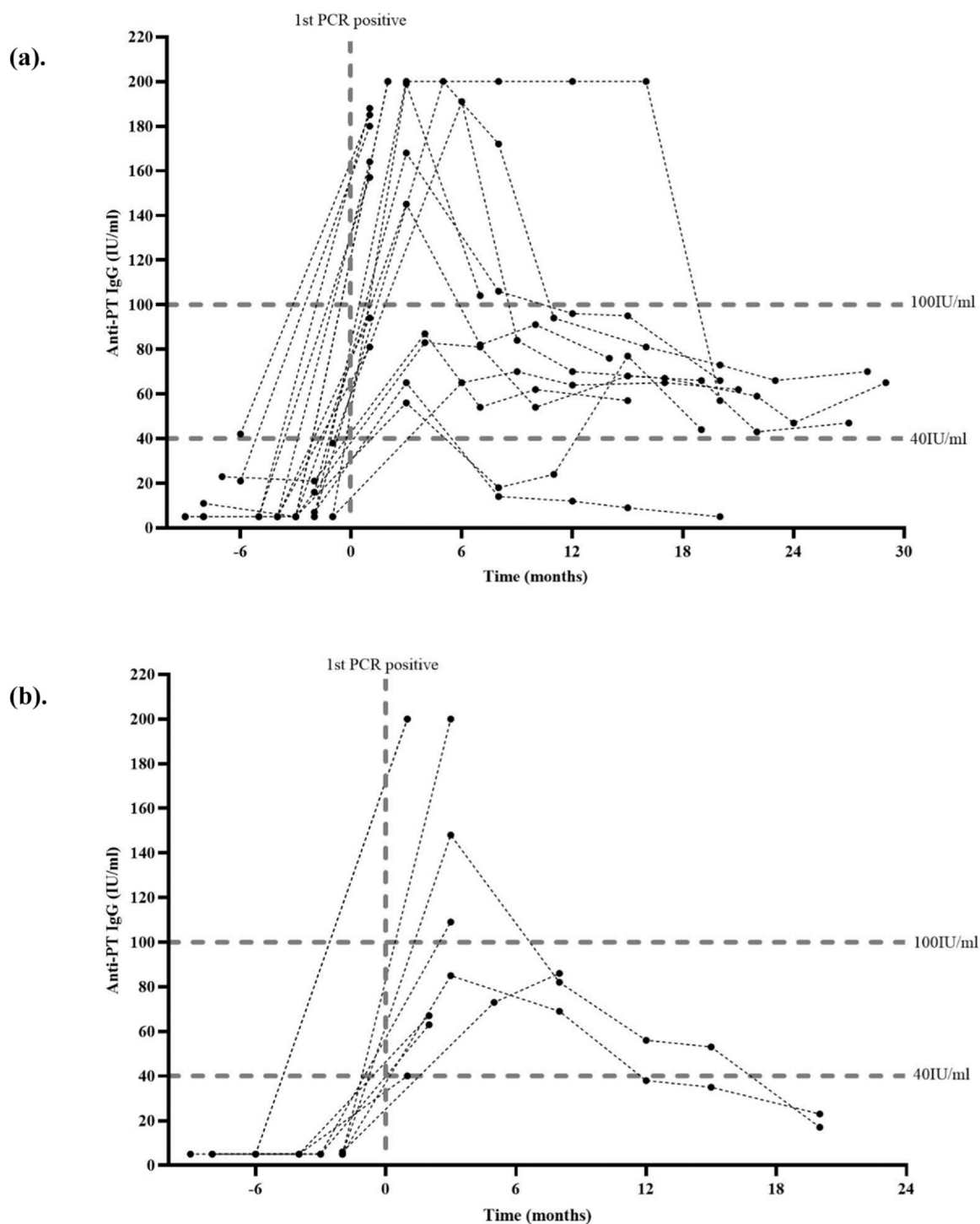


Fig. 5. Anti-PT IgG antibody titers in individuals PCR-positive for *B. pertussis* (a) assumed vaccinated with the whole-cell vaccine (n=20); (b) assumed vaccinated with the acellular vaccine (n=10), PHIRST study, South Africa, 2016 – 2018.

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Disclaimer

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships, which may be considered as potential competing interests: Fahima Mooosa reports grants from Sanofi Pasteur. Cheryl Cohen reports grants from Sanofi Pasteur, Advanced Vaccine Initiative, US Centers for Disease Control and Prevention, and the Bill & Melinda Gates Foundation; and travel fees from Parexel. Anne von Gottberg and Nicole Wolter report grants from Sanofi Pasteur, US CDC and the Bill & Melinda Gates Foundation; Neil A Martinson reports grants Bill & Melinda Gates Foundation.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2025.106550.

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