Risk factors for pertussis among hospitalized children in a high HIV prevalence setting, South Africa

N.M. du Plessis[a,*,1], G. Ntshoe[b,**,1], G. Reubenson[c], R. Kularatne[d], L. Blumberg[b], J. Thomas[b], T. Avenant[a]

[a] Department of Paediatrics, Kalafong Provincial Tertiary Hospital, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa
[b] Division of Public Health Surveillance and Response, National Institute for Communicable Diseases (NICD) of the National Health Laboratory Service (NHLS), Johannesburg, South Africa
[c] Department of Paediatrics and Child Health, Rahima Moosa Mother and Child Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[d] Department of Clinical Microbiology and Infectious Diseases, University of the Witwatersrand and NHLS Helen Joseph Hospital, Johannesburg, South Africa

A R T I C L E   I N F O

A B S T R A C T

Background: In low- and middle-income countries, including South Africa, the epidemiology of pertussis in relation to immunization, nutritional, and HIV status is poorly described. This article reports on risk factors in South African children hospitalized with pertussis.
Methods: A prospective, hospital-based, sentinel surveillance programme for pertussis was conducted in Gauteng Province, South Africa. Hospitalized children ($\leq$10 years) meeting the surveillance criteria for clinically suspected pertussis were screened and enrolled. Nasopharyngeal specimens were collected for real-time multiplex PCR and culture of Bordetella species.
Results: Bordetella pertussis was detected in 6.2% (61/992) of children. Pertussis was significantly more prevalent in infants younger than 3 months (9.8%; 38/392) and in young children between the ages of 5 and 9 years (12%; 4/34) ($p = 0.0013$). Of the 61 confirmed pertussis cases, 17 were too young for vaccination. Of the remaining 44 infants, vaccination DTP1 was administered in 73% (32/44) of pertussis-confirmed patients who were eligible, DTP2 in 50% (16/32), DTP3 in 54% (14/26), and DTP4 in 56% (5/9) of vaccine-eligible cases at 18 months of age. B. pertussis infection was less likely in children immunized at least once (5%, 32/692) than in unvaccinated children (10%, 24/230) ($p = 0.0001$). HIV exposure and infection status were determined in 978 (99%) patients: 69% (678/978) were HIV-unexposed and uninfected and 31% (300/978) were HIV-exposed. Of these HIV-exposed patients, 218 (22%) were proven HIV-exposed and uninfected and 82 patients were HIV-infected (8.4%, 82/978). HIV prevalence was similar in pertussis-positive (6%, 5/82) and pertussis-negative (6%, 55/896) children ($p = 0.90$). B. pertussis infection was unrelated to poor nutritional status.
Conclusions: In South Africa, B. pertussis poses a greater risk to infants who are too young for the first vaccine dose, those who are not vaccinated in a timely manner, and those who do not receive all three primary doses. HIV infection and HIV exposure were not associated with pertussis infection.

Introduction

Pertussis is an important global health issue. In 2015, the World Health Organization (WHO) estimated that there were 63 000 deaths from pertussis in children less than 5 years of age worldwide, mostly in developing countries (WHO, 2015a; WHO, 2015b). The Global Pertussis Initiative (GPI), an expert scientific forum addressing the international burden of pertussis, is concerned about pertussis morbidity and mortality, particularly in infants too young to be vaccinated (<6 weeks old). In all settings where surveillance is performed, these young infants carry the greatest disease burden and are at highest risk for pertussis-related complications and death (Guiso et al., 2011). Optimizing the protection of these infants requires continuous surveillance and consideration of associated risk factors (Gabutti et al., 2015).

* Corresponding author at: Private Bag X396, Pretoria 0001, South Africa.
** Corresponding author at: Private Bag x4, Sandringham, Johannesburg 2131, South Africa.
E-mail addresses: nicolette.duplessis@up.ac.za (N.M. du Plessis), genevien@nicd.ac.za (G. Ntshoe).
[1] N.M. du Plessis and G. Ntshoe contributed equally to the article.

Vaccination is the primary means of pertussis prevention, involving a three-dose primary course within the first 6 months of life (WHO, 2015b). Neither natural infection nor vaccination confers long-lasting pertussis immunity. Population-level pertussis immunity varies based on exposure to circulating *Bordetella pertussis* and waning vaccine-associated immunity (Forsyth et al., 2015). Waning immunity results in large numbers of susceptible older children and adults; when infected they act as reservoirs that may transmit pertussis to susceptible young infants (Clark, 2014). Novel control strategies have been proposed, including additional childhood boosters, vaccination of adolescents, adults and pregnant women, and vaccination of other potential transmitters including healthcare workers (Gabutti et al., 2015; Chiappini et al., 2013).

Inadequate immunization is an important risk factor globally. The anti-immunization movement in countries such as Japan, Australia, and Sweden has been associated with lower vaccination coverage and the resurgence of pertussis (Gangarosa et al., 1998). Additional risk factors in developing countries are poorly defined. It has been suggested that HIV-infected and HIV-exposed infants are at higher risk of severe pertussis infection (Muloiwa et al., 2016). In 2015, there were an estimated 6.19 million HIV-infected people in South Africa, with 18.99% of women of child-bearing age being HIV-infected (Statistics SA, 2015). South Africa has a comprehensive HIV programme, which includes the provision of life-long combination antiretroviral therapy (cART) to all HIV-infected people, including pregnant and breastfeeding women (UNAIDS, 2016). The Prevention of Mother to Child Transmission programme (PMTCT) has reduced the vertical transmission of HIV to less than 2% (SANAC Trust, 2015). Many infants are exposed to HIV but are uninfected (HEU). HEU children have higher morbidity and mortality than HIV-unexposed children (Mofenson, 2015). HEU infants are at higher risk of lower respiratory tract infections, mucocutaneous candidiasis, invasive pneumococcal disease, and both early- and late-onset group B streptococcal disease (Evans et al., 2016). The burden of pertussis in HEU children remains poorly described.

Recent hospital-based South African studies evaluating pertussis in HEU children have been inconclusive (Muloiwa et al., 2016; Nunes et al., 2016; Soofie et al., 2016). Pertussis was detected in 7% of infants hospitalized for lower respiratory tract infections in Cape Town and was detected slightly more (10.9%) in HEU infants (Muloiwa et al., 2016). The incidence of pertussis in infants in Johannesburg was lower at 2.8% of those admitted with pneumonia (Soofie et al., 2016). Most pertussis cases in these studies were in children younger than 3 months of age and in incompletely vaccinated children (Muloiwa et al., 2016; Soofie et al., 2016).

Malnutrition is associated with an increased risk of pneumonia in South African children, but it is not known whether it confers a greater risk for pertussis-associated hospitalization (le Roux et al., 2015).

The true burden of disease in South Africa is unknown and the currently available data on pertussis infection are inadequate to guide and inform future disease control and immunization policies. The aim of the present study was to contribute to the accurate documentation of prevalence of pertussis in South Africa and to determine the impact of risk factors of importance in South Africa and other low- and middle-income settings – HIV and malnutrition.

Methods

Study design and setting

The National Institute for Communicable Diseases (NICD) in South Africa maintains a hospital-based, sentinel surveillance programme for pertussis. Data collected via the surveillance programme were accessed from the paediatric departments at Rahima Moosa Mother and Child Hospital (RMMCH), Johannesburg and Kalafong Provincial Tertiary Hospital (KPTH), Pretoria, Gauteng Province, South Africa. Hospitalized children, 10 years old and younger, who met the surveillance case definition, were identified and screened. Children were enrolled from August 2013 at the Johannesburg site for a period of 27 months, and from October 2014 at the Pretoria site for a 13-month period until October 2015. A standardized case investigation form (CIF), medical records, and vaccination records were reviewed, and demographic information was gathered from these records and entered into the study database.

Case definitions

A suspected pertussis case was defined as (1) any inpatient aged ≤10 years with a cough and any one of the following: cough duration ≥7 days, paroxysms of coughing, inspiratory whoop, apnoea, cyanosis, pulse oximetry on room air ≤88%, or gagging with coughing; OR (2) any infant ≤12 months of age with apnoea. A laboratory-confirmed pertussis case was defined as a suspected case with isolation of *B. pertussis* from a clinical specimen or detection of *B. pertussis* by PCR.

Sample collection and testing

Nasopharyngeal specimens were analysed by real-time multiplex PCR, as described by Tatti et al. (2011). This assay detects IS*481* (to determine the presence of *Bordetella spp*), pIS*1001* (specific for *Bordetella parapertussis*), hIS*1001* (specific for *Bordetella holmesii*), and *ptx S1* toxin (specific for *B. pertussis*). Detection of *B. pertussis* was confirmed by detecting the *ptx S1* gene in a singleplex real-time PCR assay. A specimen was considered negative if the organism-specific targets (IS*481*, pIS*1001,* hIS*1001*, and *ptx S1*) were not detected (cycle threshold >45) and the *RNAse P* target was positive (cycle threshold ≤45).

Data management and analysis

Case patients were categorized as HIV-unexposed and uninfected (HUU), HIV-exposed and uninfected (HEU), or HIV-exposed and infected (HEI). Mothers with unknown HIV results or with no recent (in the past 3 months) results were referred to the hospital's HIV counselling and testing services. Infant diagnosis with an HIV PCR or ELISA was consequently done if the mother tested HIV-positive, depending on the child's age (younger or older than 18 months). Malnutrition was diagnosed according to the WHO growth standard weight-for-age *z*-score (WHO, 2009). Patients were underweight-for-age if the *z*-score was between −2 and −3, or severely underweight-for-age if the *z*-score was less than −3 (WHO, 2009). Prematurity was defined as a birth gestation less than 37 completed post-menstrual age weeks. The Chi-square test was used to compare the prevalence of pertussis between the categories of HIV infection and between underweight and severely underweight patients; Fisher's exact probability testing was done where case values were <5. Results were considered significant if the *p*-value was <0.05. The data analysis was done using the Stata software system.

Patients were categorized according to their eligibility for vaccination at the time of enrolment. Patients younger than 6 weeks of age were considered ineligible to have been vaccinated. The prevalence of pertussis cases was compared among patients who had received one, two, three, or four doses of pertussis vaccine. The timeliness of vaccine administration was measured in days and was calculated as the difference between the week-age

when the vaccine was administered and the upper limit of the week-age when the vaccine was recommended in the Expanded Programme on Immunization schedule. Timely vaccination was considered to have occurred if the vaccine had been administered within 4 days of the recommended week-age. Early vaccination was noted if the vaccination had been administered before 4 days of the minimum recommended week-age. Delayed vaccination was noted if the vaccine had been administered after the 4 days deemed acceptable for timely vaccination (Luman et al., 2008).

Ethical considerations

The study was approved by the Human Medical Research Ethics Committees of the University of the Witwatersrand, Johannesburg (Reference M060449) and the Faculty of Health Sciences Research Ethics Committee of the University of Pretoria (Reference 254/2014). Written informed consent was obtained from a caregiver and assent was obtained from older children in their language of choice.

Results

Study population

From August 1, 2013 to October 31, 2015, 1268 hospitalized children aged ≤10 years met the surveillance case definition and were screened. Informed consent was obtained from 1040 (82%) caregivers. Forty-eight patients were subsequently excluded due to missing laboratory results or data entry errors. Thus 992 children were included in the final analysis. Patients were included in the analysis if medical history or demographic data were available.

Data from all patients informed the epidemiological analyses. There were thus different denominator values for various outcomes.

Pertussis prevalence and detection

Most enrolled patients were younger than 1 year (70%, 693/990) and 40% (392/990) were younger than 3 months. The median age was 5.8 months (interquartile range 2.4–14.2 months). There were slightly more male patients than female patients (55%, 546/992). The most common symptoms at enrolment were cough (95%, 941/992) and fever (62%, 618/989). Prematurity was reported in 13% (125/992), asthma in 1.2% (12/988), and cardiac disease in 3.3% (33/992) of patients.

There were 78 PCR-positive results for *Bordetella spp* (8%, $n = 992$). Of these, 61 (78%) were positive for *B. pertussis*, 15 (19%) for *B. parapertussis*, and two (3%) for *B. holmesii*. *B. pertussis* was cultured from a single sample that was also PCR-positive; no other PCR-positive samples grew any bordetellae. Three *B. pertussis* samples had additional *B. parapertussis* detected.

B. pertussis detection varied significantly by age group: 9.8% (38/392) in those aged ≤3 months, 3.3% (10/301) in those aged 4–11 months, 3.4% (9/263) in those aged 1–4 years, and 12% (4/34) in those aged 5–9 years ($p = 0.0005$). Patients with *B. pertussis* had a median age of 5.9 months (interquartile range 1.9–13.4 months) (Table 1). *B. pertussis* infection was similar among females (7%, 31/446) and males (6%, 30/544) ($p = 0.34$). *B. pertussis* detection peaked in November 2014 to January 2015 and in April to August 2015, including one household cluster of two cases, but the detection rate remained constant (Figure 1).

Table 1
Characteristics of hospitalized patients enrolled in the surveillance programme for pertussis (2013–2015).

Variable	All enrolled patients n (%)	B. pertussis cases n (%)	% positive	p-Value[a]
Age				
Median (IQR) months	5.8 (2.4–14.2)	5.9 (1.9–13.4)		
Sex	n = 992	n = 61		0.34
Female	446 (45)	31 (51)	7	
Male	546 (55)	30 (49)	6	
HIV status[b]	n = 978	n = 60		0.90
HEI (all ages)	82 (8)	5 (8)	6	
≤3 months	22/82 (27)	1/5 (20)		
4–11 months	26/82 (32)	0		
HEU (all ages)	218 (22)	12 (20)	6	
≤3 months	98/218 (45)	9/12 (75)		
4–11 months	69/218 (32)	1/12 (8)		
HUU (all ages)	678 (69)	43 (72)	6	
≤3 months	263/678 (39)	27/43 (63)		
4–11 months	205/678 (30)	9/43 (21)		
Nutritional status[c]	n = 976	n = 61		0.04
Normal	683 (69)	49 (80)	7	
Any UWFA (UWFA + severe UWFA)	293 (31)	12 (20)	4	
Pertussis vaccine doses received	n = 922	n = 56		0.0003
0	230 (25)	24 (43)	10	
1	132 (14)	15 (27)	11	
2	104 (11)	4 (7)	4	
3	359 (39)	8 (14)	2	
4	97 (11)	5 (9)	5	
WHO pertussis clinical criteria	n = 990	n = 60		0.31
Yes	41 (4)	4 (7)	10	
No	949 (96)	56 (93)	6	
Outcome	n = 969	n = 61		0.05
Died	23 (2)	4 (7)	17	
Discharged	946 (98)	57 (93)	6	

IQR, interquartile range; WHO, World Health Organization.
[a] Pertussis-positive cases (*B. pertussis* cases) were compared to pertussis-negative cases (all enrolled patients minus *B. pertussis* cases).
[b] HIV status at enrolment: HEI = HIV-exposed and HIV-infected; HEU = HIV-exposed and HIV-uninfected; HUU = HIV-unexposed and HIV-uninfected.
[c] Weight-for-age at enrolment: UWFA = underweight-for-age (weight-for-age z-score between −2 and −3); severe UWFA = weight-for-age z-score of <−3).
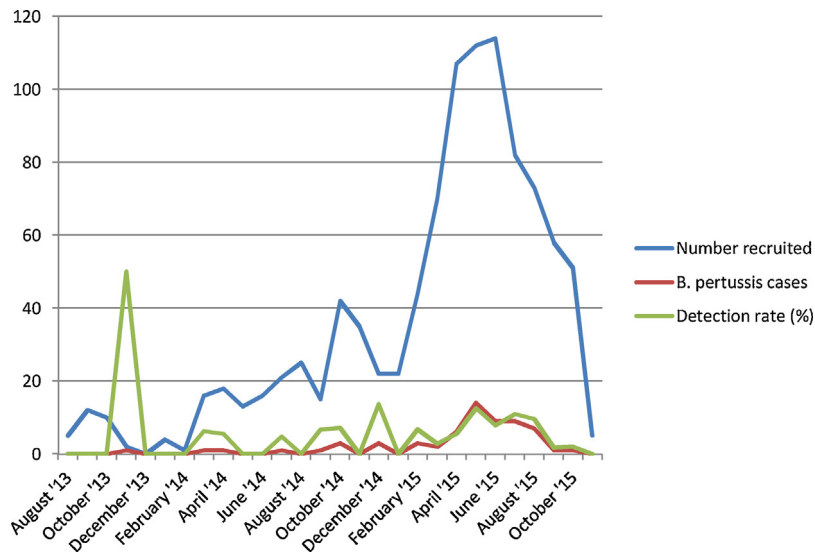
Figure 1. Enrolment of the study participants and *Bordetella pertussis* cases per month (2013–2015). Enrolment at Rahima Moosa Mother and Child Hospital started August 2013. Kalafong Provincial Tertiary Hospital started enrolling study patients from October 2014.

Vaccination status

Most enrolled patients were eligible for their first pertussis-containing vaccine (DTP) (89%, 878/991) and had received the vaccine (78%, 689/878). However, many children who were eligible for pertussis vaccination had not received certain indicated vaccine doses: unvaccinated DTP1 = 16% (127/816); DTP2 = 23% (161/715); DTP3 = 27% (167/629). An unvaccinated status was associated with a higher frequency of pertussis infection ($p = 0.0001$, Table 1).

Of the laboratory-confirmed pertussis cases, 17 (28%, $n = 61$) were younger than 6 weeks and so had not been immunized. Vaccination DTP1 was administered in 73% (32/44) of patients who were eligible, DTP2 in 50% (16/32) of patients, DTP3 in 54% (14/26) of pertussis-confirmed patients, and DTP4 in 56% (5/9) of patients at 18 months of age. The prevalence of pertussis infection decreased with increasing receipt of pertussis-containing vaccines ($p = 0.00006$) (Figure 2).

Most of the 32 patients who received DTP1 were vaccinated after 6 weeks of age (66%, 21/32). Late DTP1 vaccinations were administered at a mean of 45 days (interquartile range 44–48 days). The proportion of both missed and delayed vaccination increased with subsequent pertussis-containing vaccine doses (Figure 3).

HIV exposure and infection

HIV exposure and infection status were determined in 978 (99%) patients: 69% (678/978) were HUU and 31% (300/978) were HIV-exposed. Of these HIV-exposed patients, 218 (22%) were proven HEU and 82 patients were HEI (8.4%, 82/978). The age distribution of the HEI group showed that the smallest proportion of HEI patients were younger than 3 months old (6%, 22/383) and the greatest proportion of HEI patients fell in the 5 to 9-year-old group (38%, 13/34; $p < 0.0001$).

The pertussis infection rate was similar ($p = 0.90$) in the HIV-infected group (HEI; 6%, 5/82) and HIV-uninfected patients (HEU + HUU; 6%, 55/896) (Table 1). There was no significant difference ($p = 0.65$) in pertussis infection rate between the HEU (5.5%, 12/218) and HUU (6.3%, 43/678) groups. In patients with pertussis younger than 3 months of age, 2.1% were HEI, 19.2% were HEU, and 57.5% were HUU. Amongst laboratory-confirmed pertussis cases, 75% of HEU children were ≤3 months of age. In
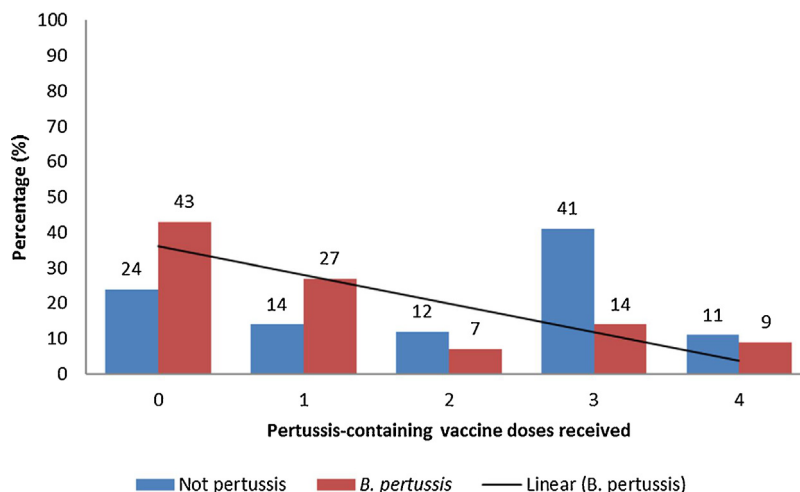
Figure 2. Total vaccine doses (%) received in both the pertussis and non-pertussis groups, and the trend of *Bordetella pertussis* cases to vaccine doses received.
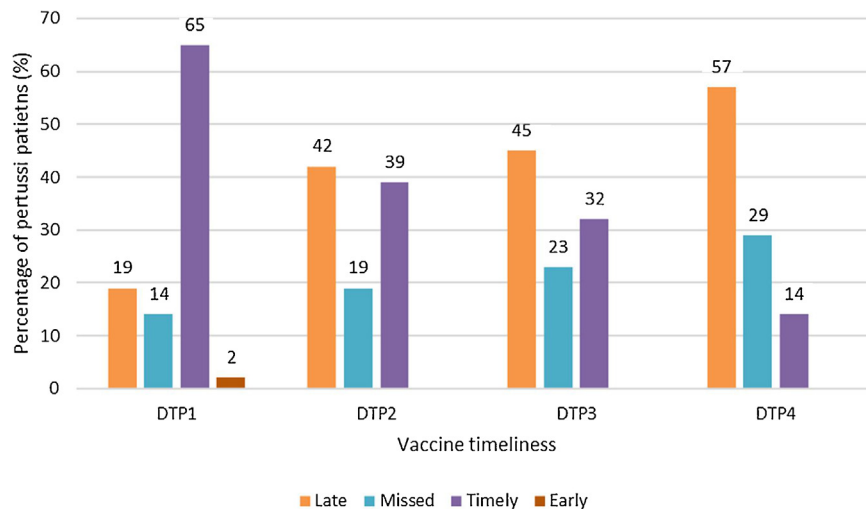
Figure 3. Vaccine timeliness of DTP1, DTP2, DTP3, and DTP4 (booster dose) in eligible patients (>6 weeks) with laboratory-confirmed pertussis.

patients who were HUU, pertussis was associated with an unvaccinated status.

Malnutrition

Approximately one-third of patients were identified as malnourished (30%, 293/976), of whom 18% (172/976) were severely underweight-for-age and 12% (121/976) were under-weight-for-age. The occurrence of *B. pertussis* infection was higher ($p = 0.04$) in patients with a normal nutritional status (7%, 49/671) compared to both underweight-for-age and severely underweight-for-age patients (4%, 12/293) (Table 1).

Other medical conditions and hospitalization statistics

B. pertussis infection was not more prevalent in patients with a history of prematurity (10%, 6/61, $p = 0.55$) or cardiac disease (2%, 1/61, $p = 0.46$). Pertussis infection was not significantly associated with chronic respiratory conditions (5%, 3/58, $p = 0.8$) or with asthma.

The WHO clinical criteria for pertussis diagnosis were applied to data captured for 990 patients (WHO, 2015a). Based on WHO criteria, only 41 (4.1%, $n = 990$) patients had clinically suspected pertussis. Equal proportions of patients with PCR-confirmed pertussis (9.8%, 4/41) and without laboratory-confirmed pertussis (5.9%, 56/949, $p = 0.31$) met the WHO criteria.

Patients were hospitalized for a median of 4 days (range 2–7 days). The duration was similar for patients with *B. pertussis* (median 5 days, range 2–11 days) and other patients (median 4 days, range 2–7 days). Nine percent (88/976) of patients were admitted to the intensive care unit. Intensive care unit admission did not differ between patients with pertussis and other patients (pertussis 13%, 8/61 vs. 8.7%, 80/915; $p = 0.30$). In-hospital fatality of all enrolled patients was 2.4% (23/969); 6.7% (4/61) of pertussis patients died compared to 2.1% (19/908) of other patients ($p = 0.03$). All pertussis-related deaths occurred in patients younger than 3 months old, and fatalities in enrolled patients without a confirmed pertussis diagnosis were also most common in infants aged <3 months (47%, 9/19), followed by those aged 4–11 months (42%, 8/19) and toddlers aged 1–4 years (11%, 2/19).

Discussion

This study analysed the prevalence of laboratory-confirmed pertussis disease in children hospitalized with respiratory infections clinically suspicious of pertussis. The success of sentinel surveillance programmes relies on consistent monitoring and reporting at strategically placed localities. PCR results confirmed pertussis infections in 6.2% of patients hospitalized for symptoms and signs suspicious of pertussis in two paediatric hospitals in Gauteng Province. The prevalence of pertussis was higher in incompletely vaccinated children and those too young for vaccination. There was no difference in pertussis infection rate between HIV-uninfected and HIV-infected children. Pertussis infection rates were slightly higher in normal weight-for-age compared to malnourished children.

Currently, in South Africa, pertussis vaccines are administered in a four-dose schedule, consisting of a three-dose primary series (6, 10, and 14 weeks) followed by a booster at 18 months. No additional pertussis-containing vaccines are routinely provided to school-age children, adolescents, or adults (Gangarosa et al., 1998).

Large disparities exist in the estimates of vaccination coverage, especially in developing countries where reporting standards are not in place. The present study corroborates the WHO and United Nations Children's Fund (UNICEF) estimate of 69% DTP3 vaccine coverage in South Africa (South Africa, 2016), necessitating comprehensive surveillance. The high detection rate of pertussis (6.2%) in this study is similar to the detection rate in infants in Cape Town who had a vaccination coverage of 85.2% (Muloiwa et al., 2016). The prevalence of pertussis decreased with increasing age and increasing number of vaccination doses received up to the age of 4 years. This pattern is expected (Muloiwa et al., 2016; Zouari et al., 2012) and meets the objectives of global immunization initiatives (Guiso et al., 2011). In South Africa, pertussis occurs mostly in infants too young to have received their first pertussis-containing vaccine (Muloiwa et al., 2016; Nunes et al., 2016; Soofie et al., 2016). The continued circulation of pertussis in South Africa indicates the presence of reservoirs in the population, potentially siblings and carers.

Booster vaccinations have been proposed to reduce the incidence of pertussis in reservoir populations. In response to a pertussis outbreak in England in 2012, the vaccination of 64% of pregnant women reduced pertussis in young infants by 90% (Amirthalingam et al., 2018). Booster vaccinations for older children and adolescents have also been proposed to counteract waning immunity, which was observed in the higher *B. pertussis* detection rate (12%) among older children in the present study. The higher pertussis detection rate in children aged 5–9 years is similar to reports of unusually large burdens of disease in children aged 7–10 years in the USA (Clark, 2014; Witt et al., 2012). Pertussis disease

in these age groups is associated with unrecognized infection and leads to significant morbidity and economic costs (Witt et al., 2012; Lee et al., 2004; Cherry et al., 2004). Pertussis incidence seems to be cyclical, peaking every 2–5 years (Clark, 2014; WHO, 1999). More *B. pertussis* cases were identified between April and August 2015, which was not seen during other autumn and winter periods and probably reflects disease periodicity rather than a seasonal effect.

Aside from vaccination coverage, timely administration of vaccinations, especially DTP1 at 6 weeks of age (42 days), may reduce the burden of disease in very young infants. Vaccination at an appropriate age provides protection (Quinn et al., 2014) and may increase long-term immunogenicity (Belloni et al., 2003). Almost half (47%, 29/61) of the study patients with pertussis had not received DTP1. Seventeen of these infants were too young for vaccination and 12 had missed vaccinations. Delayed and missed vaccinations were more common in older infants and children, potentially resulting in a large reservoir of *B. pertussis* in older children and adolescents. Delayed vaccinations or incomplete vaccination series have also contributed to the burden of pertussis disease in New Zealand (Radke et al., 2017) and Taiwan (Huang et al., 2017). Delayed vaccination increases individual susceptibility and reduces indirect protection against vaccine-preventable diseases (Peltola, 2000; Crowcroft et al., 2003).

In South Africa, the potential influence of HIV on young children is changing, with a marked reduction in vertical transmission. Other studies in similar high HIV prevalence settings have suggested an association between pertussis and HIV exposure (Muloiwa et al., 2016; Soofie et al., 2016). In Cape Town, the pertussis detection rate was slightly lower in HUU children compared to HEU and HEI children (Muloiwa et al., 2016), and in Johannesburg, the pertussis detection rate did not differ significantly (Soofie et al., 2016). The PMTCT programme has reduced the number of babies born with HIV, resulting in very few HIV-infected infants enrolled in this study. By contrast, 34 children aged between 5 and 9 years were enrolled, of whom 38% ($n = 13$) were infected with HIV. If HIV-positive and HIV-exposed patients were more susceptible to pertussis, higher rates of pertussis in the older age groups would be expected. While the data clearly show that HIV-infected and HIV-exposed infants were not at higher risk of pertussis, four children (12%, $n = 34$) aged between 5 and 9 years had confirmed pertussis and of these two were HIV-infected.

Despite extensive national nutrition and primary health care programmes initiated in the last decade, low weight for age remains one of the most common nutritional problems (Soofie et al., 2016). Low weight for age increases the burden of infectious disease in children, especially pneumonia. The study data show that, although malnutrition is still a burden amongst patients hospitalized with respiratory illnesses, it was not associated with an increased risk of pertussis. Also, no increased pertussis risk was found in children with heart disease, prematurity, or asthma.

The WHO recommends routine surveillance for pertussis in countries where DTP3 coverage is <90% (Lee et al., 2004), which likely applies to South Africa (Cherry et al., 2004). This study showed an increased risk of pertussis infection in unvaccinated infants less than 3 months old. The number of very young infants with HIV has dropped due to successful PMTCT programmes, and HIV infection is an unlikely risk factor for pertussis infection. Timely and complete vaccination remains the most important intervention to prevent mortality in very young babies.

Pertussis PCR was not performed on asymptomatic controls, therefore the population proportion of pertussis PCR-positive children is unknown. Using the modified clinical case definition, a large number of PCR-positive children were identified who would not have been investigated for pertussis if the WHO standard case definition was used. In addition, the interpretation of high cycle threshold values for the multi-copy insertion sequence IS*481* for pertussis detection is not well understood. Using a cut-off of 45 may have resulted in false-positives and overestimation of prevalence.

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Ethical approval

The study was approved by the Human Medical Research Ethics Committees of the University of the Witwatersrand, Johannesburg (Reference M060449) and the Faculty of Health Sciences Research Ethics Committee of the University of Pretoria (Reference 254/2014). Written informed consent was obtained from a caregiver and assent was obtained from older children in their language of choice.

Conflict of interest

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References

Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet 2018;384(9953):1521–8.

Belloni C, de Silvestri A, Tinelli C, Avanzini MA, Marconi M, Strano F, et al. Immunogenicity of a three-component acellular pertussis vaccine administered at birth. Pediatrics 2003;111(2):1042–5.

Cherry JD, Chang SJ, Klein D, Lee M, Barenkamp S, Bernstein D, et al. Prevalence of antibody to *Bordetella pertussis* antigens in serum specimens obtained from 1793 adolescents and adults. Clin Infect Dis 2004;39(11):1715–8.

Chiappini E, Stival A, Galli L, De Martino M. Pertussis re-emergence in the post-vaccination era. BMC Infect Dis 2013;13(1):151.

Clark TA. Changing pertussis epidemiology: everything old is new again. J Infect Dis 2014;209(7):978–81.

Crowcroft N, Stein C, Duclos P, Birmingham M. How best to estimate the global burden of pertussis?. Lancet Infect Dis 2003;3(7):413–8.

Evans C, Jones CE, Prendergast AJ. HIV-exposed, uninfected infants: new global challenges in the era of paediatric HIV elimination. Lancet Infect Dis 2016;16(6):e92–e107.

Forsyth K, Plotkin S, Tan T, von König CHW. Strategies to decrease pertussis transmission to infants. Pediatrics 2015;135(6):e1475–82.

Gabutti G, Azzari C, Bonanni P, Prato R, Tozzi AE, Zanetti A, et al. Pertussis: current perspectives on epidemiology and prevention. Hum Vaccin Immunother 2015;11(1):108–17.

Gangarosa EJ, Galazka AM, Wolfe CR, Phillips LM, Miller E, Chen RT, et al. Impact of anti-vaccine movements on pertussis control: the untold story. Lancet 1998;351 (9099):356–61.

Guiso N, Wirsing von König CH, Forsyth K, Tan T, Plotkin SA. The Global Pertussis Initiative: report from a Round Table Meeting to discuss the epidemiology and detection of pertussis, Paris, France, 11–12 January 2010. Vaccine 2011;29 (6):1115–21.

Huang WT, Lin HC, Yang CH. Undervaccination with diphtheria, tetanus, and pertussis vaccine: national trends and association with pertussis risk in young children. Hum Vaccin Immunother 2017;13(4):757–61.

Lee GM, Lett S, Schauer S, LeBaron C, Murphy TV, Rusinak D, et al. Societal costs and morbidity of pertussis in adolescents and adults. Clin Infect Dis 2004;39 (11):1572–80.

Luman ET, Shaw KM, Stokley SK. Compliance with vaccination recommendations for US children. Am J Prev Med 2008;34(6):463–70.

Mofenson LM. Editorial commentary: new challenges in the elimination of pediatric HIV infection: the expanding population of HIV-exposed but uninfected children. Clin Infect Dis 2015;60(9):1357–60.

Muloiwa R, Dube FS, Nicol MP, Zar HJ, Hussey GD. Incidence and diagnosis of pertussis in South African children hospitalized with lower respiratory tract infection. Pediatr Infect Dis J 2016;35(6):611–6.

Nunes MC, Downs S, Jones S, van Niekerk N, Cutland CL, Madhi SA. *Bordetella pertussis* infection in South African HIV-infected and HIV-uninfected mother–infant dyads: a longitudinal cohort study. Clin Infect Dis 2016;63(Suppl. 4): S174–80.

Peltola H. Worldwide *Haemophilus influenzae* type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. Clin Microbiol Rev 2000;13(2):302–17.

Quinn HE, Snelling TL, Macartney KK, McIntyre PB. Duration of protection after first dose of acellular pertussis vaccine in infants. Pediatrics 2014;133(3):e513–9.

Radke S, Petousis-Harris H, Watson D, Gentles D, Turner N. Age-specific effectiveness following each dose of acellular pertussis vaccine among infants and children in New Zealand. Vaccine 2017;35(1):177–83.

le Roux DM, Myer L, Nicol MP, Zar HJ. Incidence and severity of childhood pneumonia in the first year of life in a South African birth cohort: the Drakenstein Child Health Study. Lancet Glob Health 2015;3(2):e95–e103.

SANAC Trust. South Africa Global Aids Response Progress Report (GARPR) 2015. South African National AIDS Council Trust; 2015.

Soofie N, Nunes MC, Kgagudi P, van Niekerk N, Makgobo T, Agosti Y, et al. The burden of pertussis hospitalization in HIV-exposed and HIV-unexposed South African infants. Clin Infect Dis 2016;63(Suppl 4):S165–73.

South Africa: WHO and UNICEF estimates of immunization coverage: 2015 revision 2016 [Available from: http://data.unicef.org/wp-content/uploads/country_profiles/South%20Africa/Immunization_zaf.pdf].

Statistics SA. Mid-year population estimates, 2015. Statistics South Africa; 2015 Contract No.: P0302.

Tatti KM, Sparks KN, Boney KO, Tondella ML. Novel multitarget real-time PCR assay for rapid detection of *Bordetella* species in clinical specimens. J Clin Microbiol 2011;49(12):4059–66.

Prevention Gap Report. UNAIDS; 2016.

WHO. WHO-recommended standards for surveillance of selected vaccine preventable diseases. 1999.

WHO. WHO child growth standards and the identification of severe acute malnutrition in infants and children: a joint statement by the World Health Organization and the United Nations Children's Fund. Geneva: World Health Organization; 2009.

WHO. Pertussis vaccines: WHO position paper — Aug 2015. Wkly Epidemiol Rec 2015a;90(35):433–60.

WHO. Immunization, vaccines and biologicals. 2015.

Witt MA, Katz PH, Witt DJ. Unexpectedly limited durability of immunity following acellular pertussis vaccination in preadolescents in a north American outbreak. Clin Infect Dis 2012;54(12):1730–5.

Zouari A, Smaoui H, Brun D, Njamkepo E, Sghaier S, Zouari E, et al. Prevalence of *Bordetella pertussis* and *Bordetella parapertussis* infections in Tunisian hospitalized infants: results of a 4-year prospective study. Diagn Microbiol Infect Dis 2012;72(4):303–17.