



REVIEW

# *Bordetella pertussis* in School-Age Children, Adolescents, and Adults: A Systematic Review of Epidemiology, Burden, and Mortality in Africa

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## ABSTRACT

The Global Pertussis Initiative recommends diphtheria–tetanus–pertussis (DTP3) vaccination of infants aged < 1 year for all African countries, and recommends the vaccination of pregnant women as a primary prevention strategy. However, the role of older children and adults in the transmission of pertussis in Africa is not clear. A systematic search of MEDLINE, EMBASE, and BIOSIS was undertaken to identify studies published between 1 January 1990 and 17 June 2019, with information on pertussis epidemiology, burden of illness, and mortality in school-aged children, adolescents, and adults in Africa. Studies identified for inclusion were reviewed narratively because a statistical comparison was not possible because of the mix of methodologies used.

Studies from North Africa (Morocco, Tunisia, and Algeria) reported that although DTP4

vaccine coverage is high, severe pertussis-related complications persist in young children, vaccine-acquired immunity wanes in adolescents, and household contacts are important transmitters of infection. A serosurvey in Gambia showed that 6% of the general population had pertussis antibody levels suggesting recent infection, and studies from Senegal showed that pertussis infection was endemic despite high DTP3 coverage. During a pertussis outbreak in Ethiopia, the case fatality rate was 3.7% overall, and 6.3% among children aged 5–9 years. In a case-surveillance study in South Africa, the incidence of pertussis among hospitalized children was 526/100,000, and infection rates were higher in HIV-exposed and -infected children compared with uninfected children. In conclusion, the highest burden of pertussis in Africa is among infants, and surveillance is lacking in many African countries meaning that the burden of pertussis among infants and infection rates among older children and adults are not well reported, and likely underestimated.

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### Key Summary Points

To evaluate pertussis infection in school-aged children, adolescents, and adults in Africa, we performed a systematic literature search and review of published studies of the epidemiology, burden, and mortality of pertussis infection.

Nineteen studies were identified in African countries.

The Global Pertussis Initiative recommends diphtheria–tetanus–pertussis (DTP3) vaccination of infants aged < 1 year for all African countries, and recommends the vaccination of pregnant women as a primary prevention strategy.

Studies from North Africa reported that although DTP4 vaccine coverage is high, vaccine-acquired immunity wanes in adolescents, and household contacts are important transmitters of infection.

The highest burden of pertussis in Africa is among infants, and surveillance is lacking in many African countries meaning that the burden of pertussis among infants and infection rates among older children and adults are not well reported, and likely underestimated.

## DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.14269751>.

## INTRODUCTION

The World Health Organization (WHO) estimates that each year there are 20–40 million

pertussis cases and 300,000 pertussis-related deaths, with low- and middle-income countries (LMICs) accounting for about 90% of cases [1]. In 2014 there were an estimated 24.1 million pertussis cases globally, of which 33% were in Africa [2]. In a 5-year modelling study of global pertussis based on United Nations population estimates and WHO and United Nations International Children’s Emergency Fund (UNICEF) data on pertussis vaccination coverage, Africa accounted for the largest proportion of pertussis cases and the majority of deaths [2]. Although diphtheria–tetanus–pertussis (DTP3) is universal in all African countries, many countries fall short of the Global Vaccine Action Plan of at least 90% national coverage [3]. On the basis of WHO/UNICEF Global estimates in 2018, there were only six countries with DTP3 national coverage of less than 50%, of which one was Syria, and the others were all in Africa: Chad, Central African Republic, Guinea, South Sudan, and Somalia [3].

Mass vaccination since the start of the Expanded Programme on Immunization (EPI) in 1974 has resulted in a large decline in the global incidence of pertussis infection [1]. However, in high-income countries (HICs), where DTaP3 and DTaP4 vaccine coverage is high, pertussis has re-emerged, with cyclical outbreaks every 3–5 years reported by numerous countries globally. In both LMICs and HICs, the highest burden of severe cases is among unvaccinated or partly vaccinated infants. For example, during an epidemic outbreak in California in 2010, among 9000 pertussis cases, there were about 808 hospitalizations and 10 infant deaths [4, 5]. In a recent systematic review and meta-analysis of data from 37 LMICs, the majority of pertussis-related deaths occurred in infants aged < 6 months, and based on data published from the start of the EPI in 1974 to 2018, the overall mortality rate was 0.8% (95% CI 0.4–1.4%) and the case fatality rate was 6.5% (95% confidence intervals [CI] 4.0–9.5%) [6].

In HICs, there has been a resurgence of pertussis and a shift in the age-specific peak of notified cases away from infants and pre-school children and towards adolescents and adults [7, 8]. The resurgence of pertussis is associated

with waning immunity in older children and adult populations, thus providing reservoirs for infection, and although pertussis is usually mild and similar to a common cold in adults, infected individuals are highly contagious for about 21 days after the onset of cough, spreading infection via aerosol droplets, thus representing a substantial risk for unvaccinated or partly vaccinated infants [9]. Further factors associated with increased pertussis notifications in HICs are improved surveillance and diagnostics, as well as the emergence of pertactin-negative strains [10–13].

In several HICs, the National Immunization Programme (NIP) includes booster doses of acellular pertussis (aP) vaccine for school-aged children and adolescents, and the Global Pertussis Initiative (GPI) recommendation for aP vaccination during pregnancy has been adopted as a primary prevention strategy in Australia, Canada, South Korea, and South Africa, about 11 European countries, and nine countries in Latin America [14–17]. The GPI recommends that LMICs aim for high DTP4 coverage, and also states that aP vaccine should be given as a priority to pregnant women, yet African LMICs have limited access to aP vaccines for older populations, and national and international efforts are currently focussed on improving whole-cell pertussis (wP) vaccine delivery to young children [18, 19].

Unlike Europe and North America where the role of older children and adults in pertussis transmission has been established, little is known about the circulation of pertussis among older populations in Africa. Therefore, we performed a systematic literature search and review of published studies of the epidemiology, burden, and mortality of pertussis infection in African countries, including studies about pertussis among school-aged children, adolescents, and adults.

## METHODS

A systematic research of the literature was conducted using EMBASE, MEDLINE, and BIOSIS to identify articles about the global epidemiology, burden, and mortality of pertussis. Citations

were limited to those in English language, in humans, and published between 1 January 1990 and 17 June 2019. Terms used in the database searches are shown in Supplement 1 in the Supplementary Material. Web searches were also performed to identify relevant data from governmental, national or regulatory websites, and from non-government organisations (Supplement 2).

The areas of interest were surveillance and sero-surveillance, clinical burden, and pertussis-related mortality and case fatality rates (CFRs). Papers were excluded if they contained no data of relevance (e.g. disease other than pertussis); no data which could be categorised by age groups; a study of pertussis vaccination (e.g. adverse events related to the vaccine); single subject design; other literature reviews that contained no primary data (in these cases, reference lists were checked and potentially useful papers not identified in the original search were obtained for assessment); and based on a model (either economic or epidemiological), which included no epidemiology source for the calculations or were based on a publication already included in the search.

The review included publications with data for school-aged children, adolescents, and adults. The objective was to review the epidemiology, burden, and mortality of pertussis by age: young children (aged 4–9 years), adolescents (aged 10–18 years), adults (aged  $\geq 19$  years), and older adults (aged  $\geq 60$  years).

A total of 2190 citations were identified for the global review of epidemiology and burden. Following an initial review, 763 papers (35% of the original search) were obtained for full assessment of the inclusion criteria. The search results and reasons for exclusion are shown in Supplement 3. A total of 1421 citations were identified for the global review of mortality. Following an initial review, 331 papers (23% of the original search) were obtained for full assessment of the inclusion criteria. The search results and reasons for exclusion are shown in Supplement 4.

The systematic review was conducted to assess pertussis globally, and the results for Asia, the Middle East, and Europe are provided as

parallel publications. The search results for the global analysis are shown in Supplement 3. This paper provides the results of articles identified with relevant data from countries in Africa.

### Serological Thresholds for Infection

Polymerase chain reaction (PCR) and culture can be used to diagnose pertussis, although serology of IgG-based enzyme-linked immunosorbent assay (ELISAs) is the laboratory method that is used routinely [20, 21]. A four-fold increase in anti-pertussis toxin (PT) immunoglobulin G (IgG) agglutinin titers between samples is accepted as evidence of recent infection, and for single-sample serology, anti-PT IgG seropositivity is usually defined on the basis of the manufacturer's instructions for the ELISA test, as well as previous experience [22–24]. In individuals who have not been vaccinated within 1 year of the serum sample, anti-PT IgG  $\geq 62.5$  IU/ml to  $\geq 80$  international units [IU]/ml are often used as the cut-off thresholds indicating pertussis infection within 12 months, and cut-offs of  $\geq 100$  IU/ml and  $\geq 125$  IU/ml as evidence of recent infection and acute infection, respectively [21, 25, 26]. However, there is currently no global consensus on cut-off thresholds for single-sample serology.

### Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## SEARCH RESULTS

There were five studies which reported epidemiology data for pertussis in Africa, namely Senegal [27], Tunisia [28], Algeria [29], Nigeria [30], and Uganda [31], and seven studies which reported sero-epidemiology in Senegal [32], Cameroon [33], South Africa [34], Tunisia [35, 36], Morocco [37, 38], and Gambia [39]. There were seven studies with mortality data including Nigeria [30, 40], Ethiopia [41],

Morocco [42], South Africa [43, 44], and Senegal [27].

Six studies identified for review used PCR and/or culture to obtain laboratory diagnosis and among eight studies using ELISA, 'seropositive' and 'recent infection' were defined by a range of anti-PT IgG antibody cut-offs, yet most commonly as anti-PT IgG  $\geq 40$  IU/ml and  $\geq 100$  IU/ml, respectively.

### North Africa

There were two studies identified for Morocco, including a study of mortality data, and a hospital-surveillance study which was published as two papers, one of which was published outside the search date but was included as it was an update on a study that was included. One study was from Algeria and three were from Tunisia (Table 1).

The NIP in Algeria currently includes DTWp4 at 3, 4, 5, and 18 months [45], and the NIP in Tunisia includes DTWp4 at 2, 3, 6, and 18 months [46]. In Morocco, the current schedule includes DTWp5 at 2, 3, and 4 months, with boosters at 18 months and 5 years [38]. The studies provide data based on surveillance conducted in periods between 2007 and 2017, when DTP3 or DTP4 vaccine coverage was reported to be greater than 95% [18, 38].

### Algeria

A study in Algeria between 2012 and 2013 assessed 248 samples from patients with clinically suspected pertussis and 144 from household contacts. On the basis of diagnosis by PCR, culture, and/or serology (PT IgG  $\geq 40$  IU/ml), there were 126 cases (94%), and a further 8 cases (2%) were identified that were epidemiologically linked to a laboratory-confirmed case [29]. The median age of patients with confirmed pertussis was 3 months (range 26 days–47 years), and 82% ( $n = 110$ ) were aged  $< 6$  months, of which 52% were aged  $< 3$  months. Only 3.7% were young children or adolescents (aged 6–16 years) and 1.5% were aged  $> 16$  years. The median age of household contacts was 30 years (range 6–72 years), of which 80% were aged 20–40 years.

**Table 1** Overview of studies of pertussis in children and adults in North Africa

Country	Design, period	Age, <i>N</i> , sample type	Diagnostic test, and ELISA serological cut-off	Key findings
Algeria [29]	Prospective, population-based, case-surveillance  February 2012–September 2013	All ages 392 suspected cases	PCR, culture, and/or serology PT IgG $\geq$ 40 IU/ml  Epidemiologically linked to confirmed case	192 (49%)  8 (2%)  All confirmed cases 82% aged < 6 months 3.7% aged 6–16 years 1.5% aged > 16 years
Tunisia [35]	Prospective, case-surveillance  February 2017–March 2018	Adults/HCWs 236 hospital employees	PT IgG $\geq$ 40 IU/ml  PT IgG $\geq$ 100 IU/ml	11.4% (95% CI 7.4–15.5); mean age 39.5 years  2.5% (95% CI 0.5–4.6)
Tunisia [36]	Prospective, population-based, case-surveillance  March 2018–June 2018	3–18 years 304 random sample	PT IgG $\geq$ 40 IU/ml PT IgG $\geq$ 100 IU/ml	12.8% (95% CI 9.1–16.6%) 14.7% (95% CI 2.3–23.3%)
Tunisia [28]	Prospective, population-based, case-surveillance  2007–2016	< 10 years  1844 with respiratory tract infection and suspicion of pertussis	PCR and culture	134/100,000 children aged < 5 years
Morocco [42]	Retrospective, population-based, national survey  1988–1998	< 5 years 94 autopsy reports among representative sample of child deaths	N/A	Pertussis-related mortality rate 0.21/1000 children aged < 5 years
Morocco [37]	Prospective, case-surveillance  January 2013–June 2015	< 14 years: 156 children hospitalized for pertussis 126 household contacts	PCR	All cases aged < 5 years; 57% aged < 2 months 47% of household contacts confirmed pertussis

**Table 1** continued

Country	Design, period	Age, <i>N</i> , sample type	Diagnostic test, and ELISA serological cut-off	Key findings
Morocco [38]	Prospective, case-surveillance	< 14 years: 128 children hospitalized for pertussis	PT IgG > 100 IU/ml	<i>N</i> = 5
			40–100 IU/ml	<i>N</i> = 17
	January 2015–June 2017	140 household contacts	PT IgG > 40 and PT IgA > 12	<i>N</i> = 15
			PT IgA > 12 IU/ml	<i>N</i> = 53
Total			55/140 (39%) household contacts confirmed cases	

HCW healthcare worker, PT IgG pertussis immunoglobulin G, CI confidence interval

The primary source of exposure and transmission of infection was the mother, comprising 82% of confirmed cases and 90% of unconfirmed cases ( $p > 0.05$ ). Other close contacts made up 18% of confirmed cases [29].

### Tunisia

Based on surveillance in Tunisia between 2007 and 2011, the prevalence of PCR and/or culture-confirmed pertussis was 21% among hospitalized infants aged < 1 year, and between 2007 and 2016, the incidence of pertussis was 134/100,000 children aged < 5 years [28]. Surveillance of admissions at a children's hospital in Tunis between 2007 and 2016 showed that pertussis was prevalent and cyclical, and among 1844 children and infants hospitalized with suspected pertussis during this period, 306 had PCR-confirmed infection. Despite the intention of including children aged up to 18 years, all of the children included were aged < 10 years, and of the confirmed cases, 95% were aged < 6 months, 1.6% aged 1–5 years, and 0.7% aged > 5–10 years [28]. A seroprevalence study among healthcare workers (HCWs) at the same children's hospital during the same surveillance period confirmed that pertussis was circulating in hospital settings and affecting HCWs in close contact with infants [35]. Among 236 HCWs with a median age of 31 years, there were 27 cases (11.4%; 95% CI

7.4–15.5) with anti-PT IgG  $\geq$  40 IU/ml, with a mean age of 39.5 years. There were 6 cases (2.5%; 95% CI 0.5–4.6) with anti-PT IgG  $\geq$  100 IU/ml, and the highest titers were detected in those aged 21–40 years [35].

A serosurvey of children and adolescents in Tunisia in 2018 included 304 children with a mean age of 9.3 years, all of whom had received DTP according to the NIP. Overall, 12.8% (95% CI 9.1–16.6%) were seropositive (PT IgG  $\geq$  40 IU/ml), and 14.7% (95% CI 2.3–23.3%) had anti-PT IgG  $\geq$  100 IU/ml [36]. The population was divided by age groups: 3–5 years ( $n = 55$ ), 6–12 years ( $n = 184$ ), and 13–18 years ( $n = 65$ ), and although the highest titers were observed among children aged > 8 years, in the univariate and multivariate analyses, there was no association between age group and geometric mean anti-PT IgG titers [36].

### Morocco

A prospective study in Morocco assessed all children aged < 14 years admitted to a public hospital network in Casablanca for suspected pertussis between 2013 and 2015. The aim was to assess pertussis infection in household contacts. Among 156 children, 126 household contact were identified [37]. All of the children identified for the study were aged < 5 years and 57% were aged < 2 months of age. Among

household contacts, 47% had pertussis confirmed by PCR, many of whom reported no clinical symptoms. Further study of pertussis cases identified in hospitals in Casablanca between November 2015 and October 2017, including 128 children with pertussis and 140 household contacts. Among contacts, there were 5 cases of acute infection (PT IgG > 100 IU/ml), and 17 cases who were seropositive (PT IgG 40–100 IU/ml), but including cases identified on the basis of anti-PT IgA antibodies at a cut-off > 12 IU/ml, 55 (39%) household contacts had pertussis [38].

The only assessment of pertussis mortality in North Africa was from two national surveys on the causes and circumstances of child deaths in Morocco in 1988 and 1998 (Enquête sur les Causes et Circonstances de Décès [ECCD]-1 and ECCD-2, respectively) [42]. The surveys were based on a representative sample of deaths of children aged < 5 years (432 and 866, respectively); there were pertussis-related 6 deaths reported, giving a mortality rate of 0.21/1000 children aged < 5 years [42].

## West Africa

There were six studies from West African countries which are summarized in Table 2.

### Senegal

In Senegal between 1986 and 1987, a mass immunization campaign was conducted to improve EPI coverage among children aged < 5 years. The NIP in Senegal currently includes three doses of wP vaccine within the first year of life.

In a rural population in Senegal, from 1986 to 1993, mothers of 570 children aged 5–14 years were asked if their child had been affected by pertussis; the incidence rate of pertussis was 88/1000 person-years [27]. After the introduction of a vaccination programme, the overall incidence decreased by 27% after 3 years, and 46% after 6 years. A decline in the incidence of pertussis was observed in all age groups, but was greatest in children aged < 5 years, particularly in unvaccinated infants. The median age of people diagnosed

with pertussis increased steadily in line with population vaccine coverage [27]. In another study in Senegal, two different cohorts of children and adolescents were assessed, and in 1986, the case-fatality rate (CFR) was 0.2% among children aged 5–14 years, and 2% in children aged 2–4 years. In the second survey in 1990 there were no pertussis-related deaths in anyone aged > 2 years [27]. There was one global review including mortality data for Senegal, Argentina, Australia, New Zealand, Switzerland, and Italy [47]. For Senegal, in the population aged < 15 years, the pertussis-related mortality rate was 600/1 million [47]. For comparison, the mortality rate for Argentina (all ages) was 65.6/1 million, and the all-age mortality rate for Australia (1966–1995) was 1.1/1 million, falling to 0.36/1 million in 1996–2005.

### Gambia

A DTwP4 schedule is currently recommended in the Gambia with doses at 2, 3, 4, and 16 months.

A serosurvey was conducted in people aged 2–90 years in rural Gambia in 2008, and among a cohort of 1893, 6% had anti-PT IgG  $\geq$  62.5 IU/ml, 17.5% had anti-PT IgG 20–62.5 IU/ml, 4.4% had PT IgG > 62.5–125 IU/ml, and 1.8% had anti-PT IgG  $\geq$  125 IU/ml [39]. Higher antibody concentrations were observed in older populations, and the risk of infection increased with age (1.9% yearly increase, 95% CI 1.3–2.5). The authors concluded that *Bordetella pertussis* was being transmitted despite high vaccination coverage and that reinfection may have occurred, implying that immunity from childhood vaccination may not be lifelong [39].

### Nigeria

In Nigeria, the NIP includes DTwP3 at 6, 10, and 14 weeks, and the WHO reported that DTP3 coverage in 2018 was 57% [40, 48].

In Nigeria, based on a clinical definition, and a population of 155 young children and adolescents of undefined age (5 cases in children aged 10–14 years) [30], the overall pertussis attack rate of suspected cases was 155/11,172 (1.4%), and the CFR was 24/155 (15.5%). The authors noted that the CFR was highest in those

**Table 2** Overview of studies of pertussis in children and adults in West Africa

Country	Design, period	Age, <i>N</i> , sample type	Diagnostic test and ELISA serological cut-off	Key findings
Senegal [47]	Review of global population-based mortality rates  Search years 1945–2014	< 15 years  Published data	N/A	Mortality rate 600/1 million
Senegal [27]	Prospective, population-based, case-surveillance  January 1984–December 1996	< 15 years  6060 presented with pertussis	Clinical diagnosis: mothers' interviews from 1984 to 1987; clinical diagnosis by a physician from 1988	Crude incidence 183/1000 child-years at risk age < 5 years  Pertussis-related CFR 2.8%  After vaccination programme: incidence decreased by 27% after 3 years, and 46% after 6 years
Senegal [32]	Prospective, population-based, longitudinal cohort  October 2008–January 2010	1–9 years  410 random sample	PT IgG > 30 IU/ml  PT IgG > 80 IU/ml  PT IG ≥ 62.5 EU/ml  PT IgG > 30 IU/ml	33.6%  16.2%  6%  1–2 years: 45% ( <i>n</i> = 65) 2–3 years: 34% ( <i>n</i> = 62) 3–4 years: 19% ( <i>n</i> = 42) 4–5 years: 26% ( <i>n</i> = 27) 6–7 years: 33% ( <i>n</i> = 58) 7–8 years: 33% ( <i>n</i> = 57) 8–9 years: 37% ( <i>n</i> = 63)
Gambia [39]	Prospective, population-based, longitudinal cohort  2008	2–90 years  1893 random sample	PT IgG < 20 EU/ml    PT IgG 20–62.5 EU/ml  PT IgG 62.5–125 EU/ml  PT IgG ≥ 125 EU/ml	76.3%    17.5%  4.4%  1.8%



**Table 2** continued

Country	Design, period	Age, <i>N</i> , sample type	Diagnostic test and ELISA serological cut-off	Key findings
Nigeria [30]	Prospective, population-based December 2015	Children and adolescents 155 pertussis cases 310 unmatched controls	Clinical diagnosis	Attack rate suspected cases 55/11,172 (1.4%) Pertussis-related CFR 15.5%
Nigeria [40]	Retrospective, population-based 1973 to 1982	Not reported	Not stated	Pertussis-related CFR 1.0%

*PT IgG* pertussis immunoglobulin G, *CI* confidence interval, *CFR* case fatality rate, *EU* enzyme-linked immunosorbent assay units

aged 12–59 months. In another Nigerian study, which used national data, the pertussis CFR was 1.0%, but the age range was not reported [40].

### Central Africa and Horn of Africa

A summary of studies from Uganda, Ethiopia, and Cameroon is shown in Table 3.

#### Cameroon

In Kumba, Cameroon in 1989, a town with about 100,000 inhabitants, a serosurvey included children aged 5–14 years, who were completely unvaccinated against pertussis. Anti-PT IgG levels were assessed in 365 children, and overall, 75% were seropositive (PT IgG levels three times the mean value of negative sera [PT IgG < 80 IU/ml] obtained from young children). Seroprevalence increased significantly by age: 5 years, 62%; 6–7 years, 67%; 8–9 years, 73%; 10–11 years, 82%; and 12–14 years, 81% ( $p < 0.001$ ) [33].

#### Uganda

In Uganda, 449 children aged 3 months–12 years (50% were aged < 5 years)

with persistent cough lasting at least 14 days between July and December of 2013 were laboratory assessed for pertussis. The rate of PCR-confirmed pertussis was 15% (95% CI 12–18) and the rate of anti-PT IgG  $\geq 100$  IU/ml was 20% (95% CI 16–24), and the rate by age was 15%, 11%, and 18% in children aged 3–23 months, 24–59 months, and > 59 months, respectively; the corresponding full vaccination coverage was 84%, 93%, and 94%, respectively [31].

#### Ethiopia

In a remote district of Ethiopia with a weak surveillance system, a study reported the epidemiology of cases during an outbreak between July and October 2015. There were 215 suspected cases, at an attack rate of 1.3/1000 population [41]. A total of 57.2% were children aged < 5 years, and the mean age of cases was 3.7 years, ranging from 3 months to 45 years, at an attack rate of 29.8% among children aged 5–9 years, 3.7% among children aged 10–14 years, and 9% among those aged  $\geq 15$  years, giving an incidence of 0.09/1000 population aged 15 years. The overall CFR was 3.7%, and the highest rate was among

**Table 3** Overview of studies of pertussis in children and adults in Central Africa and the Horn of Africa

Country	Design, period	Age, <i>N</i> , sample type	Diagnostic test, and ELISA serological cut-off	Key findings
Cameroon [33]	Prospective, population-based 1989	5–14 years 367 random sample of unvaccinated children	PT IgG levels three times the mean value of negative sera obtained from young children (negative by PT IgG < 80 IU/ml)	75% Aged 5 years, 62%; aged 6–7 years, 67%; aged 8–9 years, 73%; aged 10–11 years, 82%; and aged 12–14 years, 81%; ( $p < 0.001$ )
Uganda [31]	Prospective, population-based July and December 2013	3 months–12 years 449 with cough $\geq 2$ weeks	PCR PT IgG $\geq 100$ IU/ml	15% (95% CI 12–18) 20% (95% CI 16–24) Aged 3–23 months, 15%; aged 24–59 months, 11%; aged > 59 months, 18%
Ethiopia [41]	Prospective, outbreak surveillance July and October 2015	All ages 215 cases	Clinical diagnosis	Attack rate 1.3/1000 population Mean age 3.7 years (3 months–45 years) Attack rate aged 5–9 years, 29.8%; aged 10–14 years, 3.7%; aged $\geq 15$ years, 9%

PCR polymerase chain reaction, ELISA enzyme-linked immunosorbent assay, CI confidence interval

children aged 5–9 years at 6.3%. The vaccination status of cases was 109 (50.7%), 27 (12.6%), and 19 (8.8%) receiving three doses, two doses, and one dose, respectively, with 59 (27.4%) and 1 (0.5%) unvaccinated and unknown, respectively. The authors concluded that vaccination may have been compromised because functional refrigerators were not available in the health posts [41].

### South Africa

In the Southern African region, South Africa was the only country with published epidemiology data for pertussis (Table 4). In South Africa, the NIP includes DTaP at 6, 10, 14 weeks, and 18 months. Boosters at 6 years and 12 years are recommended, but not state funded [49].

Tdap vaccine is recommended in South Africa for pregnant women during the 27th through 36th week of each pregnancy [15].

A prospective, hospital-based, surveillance study in Gauteng Province, South Africa assessed children aged < 10 years who were admitted for suspected pertussis between 2013 and 2015. Of 992 children, the median age was 5.8 months (IQR 2.4–14.2 months), 693 (70%) were aged < 1 years, and 392 (40%) were aged < 3 months [50]. Among 78 PCR-confirmed cases, 61 (78%) were positive for *B. pertussis*, 15 (19%) for *Bordetella parapertussis*, and 2 (3%) for *Bordetella holmesii*. Pertussis detection varied significantly by age: 9.8% (38/392) aged  $\leq 3$  months, 3.3% (10/301) aged 4–11 months, 3.4% (9/263) aged 1–4 years, and 12% (4/34) aged 5–9 years ( $p = 0.0005$ ). The pertussis infection rate was similar in human

**Table 4** Overview of studies of pertussis in children and adults in South Africa

Country	Design, period	Age, <i>N</i> , sample type	Diagnostic test and ELISA serological cut-off	Key findings
South Africa [51]	Prospective, population-based, case-surveillance September 2012–September 2013	< 13 years 7792 hospitalized children	PCR	Incidence 526/100,000 children hospitalized Incidence 4154/100,000 children hospitalized with LRTI
South Africa [50]	Prospective, population-based, case-surveillance August 2013–October 2015	< 10 years 992 suspected cases	PCR	78 (8%) Varied significantly by age: 9.8% aged ≤ 3 months, 3.3% aged 4–11 months, 3.4% aged 1–4 years, and 12% aged 5–9 years, ( $p = 0.0005$ )
South Africa [34]	Prospective, population-based 2013 and 2015 1990 and 1995	15–18 years 182 random samples	PT IgG > 30 IU/ml	74%
South Africa [43]	Retrospective, population-based 1992 to 1995	All ages 60,000 population	N/A	Pertussis-related mortality rate 5/1,000,000
South Africa [44]	Retrospective, case-surveillance 1985–1996	Children 19,037 hospitalized children	N/A	Pertussis-related CFR 1.1%

*PT IgG* pertussis immunoglobulin G, *CI* confidence interval, *CFR* case-fatality rate, *LRTI* lower respiratory tract infection

immunodeficiency viruses (HIV)-infected and HIV-uninfected patients [50].

The seroprevalence of *B. pertussis* in the Western Cape, South Africa, was assessed in randomly selected samples from 182 adolescents aged 15–18 years born between 1990 and 1995. The mean age of the population was 15.8 years, among which 74% were seropositive for anti-PT IgG (> 30 IU/ml), 15% were seronegative, and 11% had indeterminate results [34].

There were two studies providing information on the burden of pertussis and both were based on hospitalized children in Cape Town, South Africa. In one study, children aged < 13 years admitted to hospital over 1 year between 2012 and 2013 were swabbed if they had lower respiratory tract infection (LRTI) based on WHO-defined age-specific tachypnoea or lower chest indrawing, or apnea [51]. Although older children were eligible for inclusion, among the 460 children enrolled, the median age was 8 months (interquartile range

[IQR] 2.5–14 months). A total of 75.9% ( $n = 349$ ) were HIV unexposed, 20.0% ( $n = 92$ ) were HIV exposed uninfected, and 4.1% ( $n = 19$ ) were HIV infected. There were 23 (5.0%) PCR-confirmed cases of *Bordetella* spp., of which 17 (3.7%) were *B. pertussis*, and of the confirmed cases only 9.8% ( $n = 4$ ) were clinically diagnosed with pertussis. Other diagnoses were bronchopneumonia (36.6%), bronchiolitis (36.6%), or other LRTI (17.1%). The estimated incidence of pertussis was 526/100,000 children hospitalized, and 4154/100,000 children hospitalized with LRTI. All of the children were discharged from hospital, and the median length of stay was 2 days (IQR 1–4 days) [51].

A South African audit of autopsy reports found a mortality rate from pertussis of 5/1 million, making it the seventh highest cause of death, but the mortality rate was not broken down by age group [43]. In a large scale study of patients admitted to paediatric isolation in South Africa, there were 15 deaths among 1343 patients admitted because of pertussis, giving an overall CFR of 1.1%, but the age grouping was not clearly defined [44].

## DISCUSSION

The GPI recommends DTP3 for all African countries, as well as vaccination of pregnant mothers and, in order of priority, booster doses in older children, adolescents, healthcare professionals, and adults [19]. Apart from South Africa which includes infant aP vaccine and aP for pregnant women in the NIP [15], African infants are wP vaccinated, with limited access to aP vaccines for older children and adults, and no African countries currently include pregnant women in the NIP [6].

In this review, most of the epidemiological studies were from North African countries and South Africa where DTP4 vaccine coverage is high and pertussis surveillance is implemented. Hospital-based and population-based studies of the incidence and the seroprevalence of pertussis in North African countries show that infants are the most affected group, yet vaccine-acquired immunity waned in adolescents, and household contacts were important

transmitters of infection. Population-based studies in South Africa showed that vaccine-acquired immunity waned in adolescents, and in hospital-based surveillance studies, most of the children admitted with suspected pertussis were aged < 5 years. All other sub-Saharan countries follow a DTP3 schedule and pertussis surveillance is weak or lacking in many countries, particularly in central Africa. Surveillance in West Africa showed that after the start of vaccination, pertussis among infants decreased and the median age of reported cases increased. However, unlike HICs where studies show that there has been an increase in the age-specific peak of pertussis cases, comprehensive surveillance is lacking in many African countries meaning that the burden of pertussis among older children, adolescents, and adults is not well reported.

Morocco is the only country in North Africa to include DTP5, and despite high vaccine coverage, studies show that pertussis is not controlled in the country, and that it is prevalent among household contacts of infants. In a hospital-based study in Casablanca, 47% of household contacts of children with confirmed pertussis also had confirmed pertussis, many of whom had no clinical symptoms [37]. In a recent follow-up to the Casablanca study, among children aged < 5 years hospitalized for pertussis, of household contacts with confirmed pertussis, 87% were mothers [38].

Nigeria is the most populated country in Africa, and at nearly 200 million people, it is the seventh most populated country globally [52]. There were no studies providing incidence rates of pertussis identified in Nigeria, but the Nigeria Centre for Disease Control reported that in 2015 there were 6592 pertussis cases in the country, representing about 4.5% of global cases [48, 53]. Based on WHO estimates for 2018, national coverage of DTP3 in Nigeria was about 57%, and based on surveys of second-level administrative data in 2016, there was a wide variation in DTP3 coverage between districts, from 76% to 2.7% [3, 18]. There was one study identified in Nigeria which discussed an outbreak in Kaltungo in 2015, with an overall attack rate of clinically diagnosed pertussis cases of 155/11,172 (1.4%), of which 56.6% of were

among children aged 1–5 years. Suboptimal vaccination was a major factor in the outbreak, with 39.4% of children having received zero doses of pertussis vaccine, which was due partly to parental refusal to vaccinate, religion, and low educational status of mothers [30].

In Central Africa and the Horn of Africa, there was only one study each from Cameroon, Uganda, and Ethiopia identified for the review. The study in Cameroon was conducted 30 years ago and included a cohort of 365 totally unvaccinated children aged 5–14 years. The seroprevalence of anti-PT IgG was 75% overall, and increased significantly with age from 62% in children aged 5 years to 82% in children aged 10–11 years. The very high seroprevalence of anti-PT IgG antibodies indicated high levels of natural exposure among the community, and the study showed that children from households with nine or more members had a 2.2-fold probability of previous exposure to *B. pertussis* infection [33].

Pertussis surveillance in South Africa is better than in the rest of sub-Saharan Africa, yet pertussis is likely to be underdiagnosed and under-reported. On the basis of autopsy reports in South Africa in 1992–1995, pertussis was found to be the seventh highest cause of death [43], and in 1985–1995, the pertussis-related CFR was 1.1% [44]. The NIP in South Africa currently includes DTaP at 6, 10, and 14 weeks, and 18 months [49], and Tdap vaccine is recommended for pregnant women during the 27th through 36th week of each pregnancy [15]. In a hospital-based surveillance study in Cape Town in 2012–2013, the estimated incidence of pertussis among children hospitalized for LRTIs was 4154/100,000, and all of the children with pertussis were aged  $\leq 10$  years [51]. There were various LRTI diagnoses, notably, bronchopneumonia and bronchiolitis, and among 23 confirmed cases, only 4 had been clinically diagnosed with pertussis.

Hospital surveillance in South Africa also showed that the incidence of pertussis was higher among HIV-infected children (15.8%) and HIV-exposed/uninfected children (10.9%) than uninfected children (5.4%) [51]. Several studies show that HIV infection and exposure are associated with higher incidences of

pertussis, higher rates of hospitalization, and higher rates of pertussis-related deaths [6]. In a study of HIV-uninfected and HIV-infected women and their infants in a black-African community in South Africa, the incidence of pertussis was 7.4/1000 infant-months in HIV-exposed/uninfected infants, and 5.5/1000 in HIV-unexposed/uninfected infants [54]. The systematic review of pertussis in LMICs from the start of the EPI in 1974–2018 included ten epidemiological studies about pertussis in settings with a high HIV burden, all of which were in Africa. Based on eight studies from South Africa, and studies from Uganda and Zambia, the meta-analysis showed that the risk of pertussis increased with HIV exposure (RR 1.4; 95% CI 1.0–2.0), and with HIV infection (RR 2.4; 95% CI 1.1–5.1) [6].

Supporting the findings of the GPI's report on Africa, the results of this review show that the most important adult population in Africa for the transmission of pertussis to infants is mothers, and as such, the vaccination of pregnant women as primary prevention strategy should be prioritized [19]. Evidence from HICs which use infant aP vaccine schedules shows that maternal immunization is an effective strategy to reduce the burden of pertussis in infants, although there are limited data on maternal immunization in countries using infant wP vaccine [4, 55, 56]. There have been reports that infant wP vaccine responses are reduced after maternal Tdap vaccination [57], but a recent study in Columbia, where the NIP includes infant DTwP, showed that maternal Tdap vaccination given in the second or third trimester was safe for mother and foetus, and the high levels of vaccine-induced transplacental antibodies could potentially protect the newborn [16].

The main limitation of this review is that it provides a narrative analysis; however, epidemiological data were limited to a small number of countries, and across the studies available, it was not possible to calculate meaningful average values for any parameter. Further limitations were the variation in reporting systems, and lack of global consensus on anti-PT IgG antibody cut-offs, reflected in the use of various thresholds to define infection.

In addition, the restriction to only including English-language publications might have excluded data which was published in non-English-language journals. The strength of this review was that publications were identified using the well-recognised methodology of a systematic review using multiple databases to provide as comprehensive a review of pertussis in older populations in Africa as possible.

## CONCLUSIONS

Factors such as the burden of HIV and other infectious diseases, as well as malnutrition and poor access to healthcare, are likely to contribute to the burden of pertussis in Africa. The highest burden of pertussis in Africa is among infants, and surveillance is lacking in many African countries meaning that the burden of pertussis among infants and infection rates in older children and adults are not well reported.

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