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REVIEW

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

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ABSTRACT

Cyclic epidemics of pertussis (whooping cough) have been observed globally over the past twenty years despite high infant vaccine coverage. The resurgence of pertussis in high-income countries is partly due to waning vaccine immunity in older children and adults, as well as better surveillance and diagnostics. Moreover, in adolescents and adults, pertussis symptoms are mild and similar to common cough syndromes, meaning that it is under-diagnosed in older populations. 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 Asia. Studies identified for inclusion were reviewed narratively because a statistical comparison was not possible due to the mix of methodologies used. The results showed that in East Asia, including Japan, South Korea, China, and Taiwan, pertussis is circulating in older children and adults. Diphtheria–tetanus–pertussis (DTP4) coverage is high in East Asia, yet outbreaks observed in Japan and South Korea suggest that vaccine-acquired immunity had waned in adolescents and adults. Several school outbreaks in China show that pertussis is circulating in young children, with continued circulation in adolescents and adults. There was a lack of information from Southeast/South Asian countries, although pan-Asian serosurveys showed that recent pertussis infection was common in adolescents and in adults with persistent cough. To conclude, the circulation of pertussis in Asian countries with high DTP4 coverage supports the expansion of routine vaccination to include booster doses for children at school entry and adolescents. However, surveillance is weak or absent in many countries, meaning that the true burden of pertussis, particularly among older populations, is unknown.

Keywords: Adolescents; Adults; Asia; Burden; Children; Epidemiology; Pertussis; Whooping cough

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Key Summary Points

A systematic search was undertaken to identify published studies with information on pertussis epidemiology, burden of illness, and mortality in school-aged children, adolescents, and adults in Asia.

Forty seven studies were included.

The results showed that in East Asia, including Japan, South Korea, China, and Taiwan, pertussis is circulating in older children and adults.

Several school outbreaks in China show that pertussis is circulating in young children, with continued circulation in adolescents and adults. There was a lack of information from Southeast/South Asian countries, although pan-Asian serosurveys showed that recent pertussis infection was common in adolescents and in adults with persistent cough.

Surveillance is weak or absent in many countries, meaning that the true burden of pertussis, particularly among older populations, is unknown.

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.14261357.

INTRODUCTION

Bordetella pertussis is a highly contagious gram-negative bacterium that infects the respiratory tract and causes severe coughing (whooping cough). Vaccination against pertussis began in the 1950s and the use of modern-day vaccines and global immunization efforts have resulted in a large reduction in pertussis-related childhood mortality [1]. Vaccine coverage of three doses of diphtheria–tetanus–pertussis vaccine in the first year of life (DTP3) is 85–86% in most countries, and numerous countries include a pre-school booster and an adolescent booster in their national immunization programmes (NIPs) [2]. Yet despite high vaccine coverage, pertussis persists globally with cyclical epidemics every 3–4 years [3].

Pertussis can be severe in infants and is associated with substantial morbidity, yet in adolescents and adults, pertussis usually manifests as a mild respiratory illness meaning that it is largely under-recognized in adults [1]. Moreover, studies among highly vaccinated populations show that vaccine immunity wanes, resulting in a pool of unprotected adults, providing a reservoir for infection [4–6]. In several high-income countries with high childhood vaccination coverage, the age-specific peak of notified pertussis cases has shifted away from infants and pre-school children and towards adolescents and adults [7, 8]. Reasons for the increased prevalence of pertussis observed among older populations include, in addition to the waning of vaccine-acquired immunity, improved surveillance and awareness of pertussis among adults, and improved diagnostics [3]. Vaccine-driven evolution of *B. pertussis* strains that do not express pertactin is another factor that could contribute pertussis epidemics [9–11]. In several countries with high vaccine coverage, pertactin-deficient strains have been reported, including Australia where the proportion of isolates that were pertactin deficient increased from more than 10% to approximately 80% between 2008 and 2012 [9, 10, 12].

Nearly 60% of the global population lives in Asia, with China and India alone comprising 36% of the total [13]. In a global modelling study, it was estimated that in Southeast Asia in 2014, 3.5% of children aged < 5 years were infected with pertussis, equating to 6.3 million cases and 42,500 deaths [14]. The World Health Organization (WHO) estimates among children aged < 5 years in Southeast Asia, including Bangladesh, India, Indonesia, and Thailand, show that over the past 5 years, after measles,

diphtheria, and mumps, pertussis was the most frequently reported vaccine-preventable disease, with cyclical peaks; the highest number of cases was in 2016 (43,141) and the lowest was in 2019 (12,052) [15]. WHO estimates of childhood diseases in the Asia–Pacific region include high-income countries such as Australia, New Zealand, and Japan, as well as several low- and middle-income countries (LMICs) such as Malaysia, China, Cambodia, and Vietnam [16]. Among children aged < 5 years in the Asia–Pacific region, apart from 2019, when measles and pertussis were the most frequent vaccine-preventable diseases, in the past 5 years, mumps was the most prevalent vaccine-preventable disease, followed by pertussis and measles, as second and third, depending on the year. The highest number of pertussis cases in the past 5 years in the Asia–Pacific region were reported in 2019 (63,483) and the lowest year for cases was 2017 (27,624) [16]. Surveillance systems are weak in some Asian countries, yet available data show that the burden of pertussis in infants and young children is high in Asian countries [17]. However, much less is known about the prevalence of pertussis in older children and adults, and the role of this population in the transmission of pertussis across Asia.

This systematic literature search and review of published studies was performed to assess the epidemiology, burden, and mortality of pertussis infection among school-aged children, adolescents, and adults in Asia.

METHODS

A systematic research of the literature was conducted using EMBASE, MEDLINE, and BIOSIS, on 17 June 2019 to identify articles about the global epidemiology of pertussis and the burden of disease such as morbidity and mortality, healthcare usage, and hospitalization.

Citations were limited to those in English language, in humans, and published since 1 January 1990. 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 epidemiology and sero-epidemiology, clinical burden, and pertussis-related mortality and case fatality rates (CFRs). Papers were excluded if they contained no data of relevance (e.g. not a pertussis study); 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 (e.g. case studies); 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 ≥ 19 years), and older adults (aged ≥ 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 Europe, the Middle East, and Africa, are provided as parallel publications. This paper provides the results of articles identified with relevant data from countries in Asia.

There was a wide variation in the methods used to assess the epidemiology and sero-epidemiology of pertussis regarding national reporting rules, surveillance methods, clinical

diagnostic criteria, laboratory tests, antibody cut-off values, and reporting years, i.e. epidemic and interepidemic. The differences between studies meant that it was not possible to perform any formal analyses (e.g. meta-analysis) using combined data from multiple studies for any parameter, so a narrative review was performed.

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 12 studies of epidemiology in Asia covering China [18–20], Taiwan [21, 22], Japan [23–26], South Korea [27, 28], and India [29]. There were 37 studies of sero-epidemiology in Asia covering China [18–20, 30–39], Taiwan [21, 22, 40–42], Singapore [43, 44], Japan [23–26, 45–49], South Korea [28, 50–53], Thailand [54], and multiple countries [55, 56].

There were five studies about burden in Japan [57–61], four in South Korea [28, 62–64], one in India [29], and one which included three Asian countries (Taiwan, Malaysia, and Thailand) [55].

There were no studies with mortality data specifically for the populations considered in the review.

Serological Thresholds for Infection

Polymerase chain reaction (PCR) and culture can be used to diagnose pertussis, although serology of IgG-based enzyme-linked immunosorbent assays (ELISAs) is the laboratory method that is used routinely. An International consensus meeting in 2007, recommended that pertussis toxin (PT) should be used as antigen and that the results should be expressed in international units (IU/ml) using WHO international standards [65, 66]. Whereas a fourfold increase in anti-PT immunoglobulin G (IgG) agglutinin titers between samples is accepted as evidence of recent infection, there is currently no global consensus on cut-off thresholds for single-sample serology.

The thresholds for anti-PT IgG seropositivity are usually defined on the basis of the manufacturer's instructions for the ELISA test, as well as previous experience [67–69]. In individuals who have not been vaccinated within 1 year of the serum sample, anti-PT IgG $\geq$ 62.5 to $\geq$ 80 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 [66, 70, 71]. However, using data from three separate studies in Europe, receiver operator curves showed that the cut-off threshold with optimal sensitivity and specificity may be in the range between 60 and 75 IU/ml [67].

Various serological thresholds were used in the studies identified for review. In the pan-Asia studies, the anti-PT IgG cut-offs were $\geq$ 62.5 IU/ml and $\geq$ 100 IU/ml, and in Japan, the majority of studies defined the cut-off for pertussis infection as anti-PT IgG $\geq$ 100 IU/ml. In China, the majority of studies defined recent infection as anti-PT IgG $\geq$ 80 or $\geq$ 100 IU/ml, one study as anti-PT IgG $\geq$ 62.5 IU/ml, and several studies used lower thresholds, ranging from anti-PT IgG $\geq$ 16 to $\geq$ 40 IU/ml. Several studies used ELISA yet did not state the cut-off value, and some studies diagnosed pertussis using PCR and/or culture.

EAST ASIA

Most of the articles identified for review were from East Asia, including Japan (Table 1), China (Table 2), Taiwan, and South Korea (Table 3).

Japan

The vaccination schedule in Japan includes DTP at 3, 5, 6, and 18 months, yet the routine national immunization program (NIP) does not currently include boosters for adolescents, pregnant women, and adults [72, 73].

Table 1 Overview of studies of pertussis in children and adults in Japan (by publication date)

Citation	Design, period	Age, *n*, sample type	Test and serological cut-off value	Key findings
[45]	Retrospective, National Serum Reference Bank surveillance 2015 to 2016	1–60 years 460 random sample	PT IgA seropositive PT IgM seropositive	17.6%, 46–50 years 39.5%, 11–15 years
[23]	Retrospective, national pertussis surveillance 2000 to 2016	All ages Population	Sentinel data Diagnostic criteria not stated	Pertussis prevalence 2001: 27% aged 6–11 months; 3% aged ≥ 20 years 2010: 48% aged ≥ 20 years; 4% aged 6–11 months 2000–2015: 48,783 cases
[47]	Prospective, population-based 2013 and 2014	12–13 years 3243 random paired sample	PT IgG ≥ 100 EU/ml PT IgG ≥ 100 EU/ml	2013: 4.4% 2014: 3.7%
[24]	Retrospective, outbreak surveillance (outpatient facility) October 2013 to April 2014	Adults 19 haemodialysis patients 19 HCW	Highly positive: PT IgG ≥ 100 EU/ml Positive PT IgG: 10–100 EU/ml Negative PT IgG: < 10 EU/ml	*n* = 0 *n* = 16 *n* = 22
[60]	Retrospective, outbreak surveillance (university) April 2010	Young adults 636 students	Clinical diagnosis PT IgG > 100 EU/ml	245 persistent cough 84/636 'probable' infection (13.2%) 24/636 (3.7%)
[59]	Retrospective, case surveillance Circa 2013	Adults 48 confirmed cases 20 controls	PT IgG > 100 IU/ml or twofold change in PT IgG	Duration of cough at first visit 1.21 ± 1.33 months (vs control p = 0.0262) All duration of cough 2.03 ± 1.25 months (vs control 0.049) Paroxysmal cough 47.8% (vs control 0.0485) Post-tussive vomiting 30.4% (vs control 0.999)

Table 1 continued

Citation	Design, period	Age, *n*, sample type	Test and serological cut-off value	Key findings
[48]	Prospective, outbreak surveillance (workplace) May–June 2010	21–56 years 4 staff 5 household contact suspected cases	PT IgG > 100 EU/ml Antibody titer ≥ 1:320 for Yamaguchi strain	Pertussis infection 7/9 4 showed seroconversion against Yamaguchi strain
[61]	Prospective, outbreak surveillance (university) 2007	Adults 361 students and staff with cough	Agglutination antibody titer ≥ 40-fold increase	Antibody levels significantly different ($p < 0.001$) between healthy people and patients for Yamaguchi strain but not Tohama strain
[58]	Prospective, hospital-based, case surveillance March 2009	≥ 20 years 316 clinical cases	Cut-off not stated	26 confirmed cases aged 23–78 years 68% long-lasting cough 69.2% night cough 54% paroxysmal cough 19% vomiting 19% 7.7% whooping 7.7%
[46]	Prospective, medical staff Circa 2008	25–58 years 48 doctors and nurses	Agglutination antibody titer ≥ 40-fold increase FHA IgG ≥ 10 EU/ml PT IgG ≥ 10 EU/ml	81.3% (Tohama strain); 71.9% (Yamaguchi strain) 68.8% 43.8%
[49]	Retrospective, hospital-based January to May 1996	0–80 years 320 random sample	PT IgG ≥ 10 EU/ml	Three age-specific peaks: aged 11–15 years, aged 46–50 years, and aged 56–60 years
[25]	Prospective, hospital-based, case surveillance November 1986 to October 1992	All ages 1521 LRTI	> fourfold increase in titers on agglutination test between the acute and convalescent phase sera	43.9% (668) confirmed cases

Table 1 continued

Citation	Design, period	Age, *n*, sample type	Test and serological cut-off value	Key findings
[57]	Prospective, outbreak surveillance (school) May to August 1987	11–12 years 43/38 (full class or vaccinated)	Fourfold increase in titers of paired sera from one of PT IgG, FHA IgG, or agglutination test	Attack rate 7/38 (18.4%) 8 with paroxysmal coughing for > 3 weeks
[26]	Prospective, outbreak surveillance (care facility) December 1989	8–25 years 50 residents 43 carers	Positive culture, or fourfold increase in PT IgG, FHA IgG, or agglutination antibody titer in paired sera, or PT IgG ≥ 10 EU/ml, FHA IgG ≥ 20 EU/ml, or agglutination antibody titer ≥ 160-fold	Residents 82% (41) serological evidence of infection 56% (28) developed symptoms Carers 14% (6) developed symptoms, 4/6 had serological evidence of infection

PT IgG pertussis immunoglobulin G, *PT IgA* pertussis immunoglobulin A, *PT IgM* pertussis immunoglobulin M, *FHA* anti-filamentous haemagglutinin, *LRTI* lower respiratory tract infection

DTP4 coverage in Japan is more than 98%; however, between 1975 and 1981, wP was not used in Japan because of adverse neurological effects, and although an aP vaccine was introduced, many Japanese adults born during 1975–1981 did not receive vaccination [24].

Until 2017, the National Epidemiological Surveillance of Infectious Diseases in Japan monitored pertussis through paediatric sentinel sites, but because this did not represent the entire population, in 2018, the Infectious Disease Control Law was revised to include pertussis as a notifiable disease requiring laboratory-confirmed diagnosis [45].

Active Surveillance

In a study of an outbreak in an outpatient healthcare facility between October 2013 and January 2014, among 19 haemodialysis patients and 19 associated healthcare workers (HCWs), the prevalence rate was 42% among ELISA-confirmed cases [24]. In another study of HCWs on a ward with a suspected pertussis outbreak in 2007, among 48 HCWs with a mean age of 33 years, the rates of bacterial agglutination antibody positivity rates against the vaccine strains Tohama and Yamaguchi were 81.3% and 72.9%, respectively, and levels of anti-PT and anti-FHA IgG (both ≥ 10 endotoxin units [EU]/mL) were 43.8% and 68.8%, respectively [46].

In an analysis of paired serum samples from 3243 Japanese junior and senior high school students collected in 2013 and 2014, the average decrease in anti-PT IgG levels was 35% between the 2 years [47]. In the 2 years, respectively, 4.4% and 3.7% of the students had anti-PT IgG levels of ≥ 100 EU/ml. The local foci of at least fourfold anti-PT IgG increase in specific schools suggested that pertussis circulation persists in Japanese adolescents [47].

In a retrospective analysis of an outbreak at a university in Japan in 2010, among 636

students, 245 students (mean age 20.4 years) reported persistent cough, of which 84 (13.2%) were diagnosed as 'probable' cases based on clinical criteria [60]. The duration of cough was commonly more than 2 weeks, and the most common symptoms were paroxysmal cough, followed by post-tussive vomiting. Among the 245 students with continuous cough, 121 visited a healthcare provider, and 56 were diagnosed with pertussis by a physician. Among students who had received four doses of DTaP, the attack rate of 'probable' infection was 13.8% compared with 33% among unvaccinated students, and a significantly higher proportion of unvaccinated than vaccinated students reported coughing paroxysms. However, the seroprevalence of anti-PT IgG levels $\geq$ 100 EU/ml after the outbreak was similar in unvaccinated and vaccinated students [60].

Passive Surveillance

In the most recent sentinel surveillance study in Japan, between 2000 and 2015 there were 48,783 notified cases, and over time, there was a change in the age-specific proportion of cases [23]. In 2001, 27% (n = 471) of the cases were aged 6–11 months and 3% (n = 49) were aged $\geq$ 20 years, yet by 2010, those aged $\geq$ 20 years accounted for 48% (n = 2607) of cases and those 6–11 months for 4% (n = 205) [23].

When the Infectious Disease Control Law in Japan was revised to include a laboratory-confirmed diagnosis, a seroprevalence study was conducted to assess serodiagnostic tests for PT immunoglobulin A (IgA) and PT immunoglobulin M (IgM). A seroprevalence study was conducted to assess serodiagnostic tests for PT IgA and PT IgM using serum samples from a cross-section of healthy Japanese people collected between 2015 and 2016 [45]. The analysis of age-specific distribution showed that the highest anti-PT IgA levels were observed in adults aged 46–50 years (6.0 $\pm$ 6.3 NovaTec test units [NTU]), and the highest anti-PT IgM levels were found in school children aged 11–15 years (7.9 $\pm$ 3.2 NTU). A total of 17.6% of people aged 46–50 years were seropositive (> 11.5 NTU) for anti-PT IgA. Anti-PT IgA levels increased with age, and there was a significant correlation between anti-PT IgA and anti-PT IgG in adults aged 41–45 years ($p < 0.001$) [45]. The authors' concluded that the IgA and IgM assays had low diagnostic accuracy, with weak correlations with anti-PT IgG and anti-FHA IgG. The low specificity, particularly with the anti-PT IgM kit, and the arbitrary cut-offs with no thresholds for recent infection versus vaccination, means that the assays are of limited value for pertussis diagnosis [45].

China

Diphtheria toxoid combined with tetanus and whole-cell pertussis vaccines (DTwP) was introduced in China in 1978, and was replaced with diphtheria toxoid combined with tetanus and acellular pertussis vaccines (DTaP) in 2007 [74, 75]. The NIP in China currently mandates DTP at 3, 4, and 5 months, and at 18–-24 months. There are limited data on DTP4 coverage in China, yet surveillance studies in urban populations report coverage of about 95% [19, 36].

China has a large national surveillance system to monitor 39 notifiable diseases, with all hospitals and clinics obliged to report suspected and confirmed cases to the local Center for Disease Control (CDC) [76]. The data are collected on the National Infectious Diseases Monitoring Information System Database, which was established in 2004 [76].

Children and Adolescents

In a school outbreak in China in 2015, among 383 students (aged 7–13 years) and 27 teachers in ten classes, the rate of laboratory-confirmed pertussis (PT IgG $\geq$ 80 IU/ml) among students was 30.29% and among teachers was 7.41% [19]. In students in one class, the attack rate was 68.42% (26 cases), and ranged from 7.89% to 57.5% in the other classes. All of the students had received DTaP4 or DTwP4, and those who had received the last dose more than 4 years ago versus within 4 years were three times more likely to become ill with pertussis (p = 0.006). The pertussis attack rates were not significantly different between students who had received aP or wP vaccine [19]. In another school outbreak

Table 2 Overview of studies of pertussis in children and adults in China (by publication date)

Country	Design, period	Age, *n*, sample type	Test and serological cut-off value	Key findings
[122]	Prospective, hospital-based, case surveillance Jan 2016 to May 2017	1 month to 11 years 312 suspected cases	PT IgG ≥62.5 IU/ml	97 (31.1%)
[35]	Prospective, population-based 2009–2017	All ages 3360 random sample	PT IgG ≥16 EU/ml	69.9% (95% CI 68.3–71.5)
[36]	Prospective/ retrospective, population-based October to November 2015	1–59 years 1080 healthy people	PT IgG >100 IU/ml	1.17% (11/944) Incidence: 7290/100,000 Peaks: aged 7–14 years (9971/100,000) and ≥20 years (13,898/100,000)
[19]	Prospective, school cohort (outbreak) May to July 2015	School children and teachers 383 students, 27 teachers	PT IgG ≥80 IU/ml	116 (30.29%) students 2 teachers
[20]	Prospective, school cohort (outbreak) March 2016	6–12 years 94 suspected cases	PCR positive for IS481 and/ or ptxS1 but negative for hIS 1001 and pIS 1001	17 confirmed cases
[30]	Prospective, population-based May to December 2010	20–39 years 837 random sample	PT IgG undetectable PT IgG ≥40 IU/ml PT IgG ≥100 IU/ml	124 (13%) 46 (5.1%) 9 (1%)
[31]	Prospective, population-based September 2014 to October 2014	All ages 2107 random sample	IgG-PT ≥30 FDA-U/ml IgG-PT ≥80 IU/ml	33.32% Significant among age groups (p<0.0005) 169 (9.90%) Aged ≥3 years 9.9%

Table 2 continued

Country	Design, period	Age, *n*, sample type	Test and serological cut-off value	Key findings
[39]	Prospective, population-based, active surveillance 2010 to 2012	0-76 years 1825 random sample	PT IgG >30 IU/ml	49.15% Age years (*n*): 0–1 (192): 57.29% 2–3 (174): 57.47% 4–6 (178): 28.65% 7–12 (180): 28.89% 13–15 (190): 44.74% 16–20 (175): 44.00% 21–30 (193): 52.85% 31–40 (182): 57.14% 41–50 (177): 58.19% 51–76 (184): 61.41%
[18]	Prospective, population-based, case-surveillance January 2010 to December 2012	All ages 1089 suspected cases	Positive culture; positive PCR test; 4-fold increase in for paired sera; or a single serum PT IgG >580 IU/ml (if not vaccinated during 3 years)	113 confirmed cases; annual incidence 23.52/100,000 Aged 7– years, annual incidence: symptoms-based 64.76/100,000; hospital screening 2.69/100,000 Aged 16–59 years, annual incidence; symptoms-based 10.58/100,000; hospital screening 0.24/100,000
[78]	Prospective, population-based Circa 2015	0–74 years 2147 random sample	PT IgG ≥28 IU/ml	Overall, 66.28%: Aged <1 year: 22.23%; Aged >10 years: 10.19–13.51%
[75]	Retrospective, population-based October 2012 to June 2013	3–18 years 1032 stored serum from routine child clinic visits	PT IgG ≥0.1 IU/ml (full protection)	248 (42.25%) Aged 11 years versus 6 years: 93.68% versus 69.84%; $p<0.001$

Table 2 continued

Country	Design, period	Age, *n*, sample type	Test and serological cut-off value	Key findings
[33]	Prospective, clinic-based, population-based October 2013 to June 2013	3–18 years 1032 random sample	PT IgG ≥40 IU/ml PT IgG ≥100 IU/ml	101 (9787/100,000) 35 (3390/100,000)
[77]	Prospective, population-based September 2010	0–95 years 1313 random sample	PT IgG ≥30 IU/ml	117 (8.91%) 9395/100,000 population >7 years 11,561/100,000 population 41–50 years 11,428/100,000 population 13–19 years
[34]	Cross-sectional sero-epidemiological survey 2011	0–86 years 1080 healthy individulas	PT IgG >30 U/ml	Of the 850 subjects older than 4 years of age, 56 (6.6%) had anti-PT IgG titers ≥30 IU/ml, and 11 (1.3%) had titers ≥80 IU/ml The highest proportion of anti-PT IgG titers ≥30 IU/ml occurred in the 31–40 years age group
[32]	Prospective, hospital-based, case surveillance November 2008 to October 2009	2–20 years 1616 suspected cases	PT IgG >50 U/ml (40 FDA-U/ml)	(4.0%) 7000/100,000 population aged 3–20 years Peak incidences: Aged 6–8 years; 9100/100,000 per year Aged 12–20-years; 14,600/100,000 per year

PT IgG pertussis immunoglobulin G, *GM* geometric mean, *FHA* anti-filamentous hemagglutinin, *LRTI* lower respiratory tract infection, *CI* confidence interval

in Xi'an China in 2016, the prevalence of pertussis was found to be 22% among 94 children aged 11–12 years [20].

In a study between 2008 and 2009 of 1616 serum samples from children and adolescents aged 2–20 years, the seroprevalence of anti-PT IgG ≥ 40 Food and Drug Administration (FDA)-U/ml in those aged ≥ 3 years was 4.0% (95% confidence intervals [CI] 3.0%, 5.0%), which was equivalent to an estimated incidence of *B. pertussis* infection of 7000 (95% CI 5300–8800)/100,000 per year in the year before serum sampling. There were two peaks of estimated incidence: 9100 (95% CI 4300–14,000)/100,000 population per year the population aged > 6 to 8 years, and 14,600 (95% CI

Table 3 Overview of studies of pertussis in children and adults in Taiwan and South Korea (by publication date)

Country	Design, period	Age, *n*, sample type	Test and serological cut-off value	Key findings
Taiwan [21]	Retrospective, population-based, surveillance 2003 to 2017	All ages 668 confirmed cases	Culture and PCR	Mean no. cases 45/year Mean incidence 0.19 cases/100,000 population Aged 1–4 years, 0.46/100,000 population Aged 5–9 years, 0.14/100,000 population Aged 15–39 years, 0.39/100,000 population Aged ≥ 40 years, 0.03/100,000 population
Taiwan [41]	Prospective, population-based September 2012 to June 2013	Elementary school 936 random sample students	PT IgG > 11 NTU	98.89% received ≥ 3 doses DTaP vaccine Seropositive rate school grade 1, 49.36% Seropositive rate school grades 1–4 significantly higher than grade 5–6 (37.18% vs 27.56%, $p = 0.002$)
Taiwan [42]	Prospective, population-based 2013	Elementary and junior high school children and adolescents 2782	PT IgG > 11 NTU	42.5% Grade 1–3, 43.6–48.8%; grade 4–5, 26.6–28.7%; grade 6–9, 51.3%
Taiwan [22]	Retrospective, population-based, case-surveillance 1993 to 2004	All ages 2452 confirmed cases	Culture	2001–2004: incidence < 10/1 million population 1993–2004: incidence decreased with increasing age Aged 1–9 years: incidence 2–67 cases/1 million Aged 10–14 years: incidence increased from 1/1 million in 1994 to 15/1 million in 2004 ($p = 0.03$)

Table 3 continued

Country	Design, period	Age, *n*, sample type	Test and serological cut-off value	Key findings
South Korea [51]	Prospective, hospital-based 2011	21–67 years 398 HCWs	PT IgG 5–40 IU/ml	121 (30.4%)
			PT IgG Ab 40–100 IU/ml	10 (2.5%) More frequently observed in aged > 50 years vs < 50 years (p = 0.017)
			PT IgG > 100 IU/ml	3 (0.8%) levels > 100 IU/mL: acute infection
			anti-PT IgA level ≥ 125 IU/ml	0
South Korea [52]	Prospective, hospital-based surveillance July–December 2012	Aged ≥ 11 years 1192 residual sera	PT IgG > 24 EU/ml	41.4% 46.5% ≥ 51 years 39.1% < 51 years Older vs younger, p = 0.017
South Korea [53]	Prospective, hospital-based, case-surveillance December 2009 and December 2011	11–20 years and ≥ 21 years 310 with persistent cough of 1–8 weeks	Culture and/or PCR	73 (24.5%) 20/86 aged 11–20 years Mean cough duration 11.35 ± 33.3 days 56/224 aged ≥ 21 years Mean cough duration 18.43 ± 4.04 days
South Korea [27]	Retrospective, population-based passive and active surveillance 2001–2012	All ages Population	Clinically suspected pertussis	2001–2012: passive surveillance 416 cases, highest age-specific incidence in infants aged < 1 year In 2011–2012, highest age-specific incidence in groups aged > 20 years and aged 15–20 years
South Korea [28]	Prospective, hospital-based, case-surveillance July 2011 to June 2012	44.4 ± 15.9 years 622 with bothersome cough	PCR	Median cough duration was 15.0 days 35 (6.1%) PCR-confirmed Sputum, rhonchi, and post-tussive vomiting more common in patients with a positive PCR than those without (p = 0.005, p = 0.007, and p = 0.036, respectively)

Table 3 continued

Country	Design, period	Age, *n*, sample type	Test and serological cut-off value	Key findings
South Korea [62]	Prospective, case-based, hospital surveillance September 2009 and April 2011	45.9 ± 15.2 years 934 with bothersome cough	Isolation of *B. pertussis* or PCR	607 cough lasting ≥ 2 weeks 504: fulfilled clinical criteria probable case 5 PCR-confirmed Sputum, rhinorrhoea, and myalgia were less common and dyspnoea was more common in patients with a positive PCR than those without ($p = 0.037$, $p = 0.006$, $p = 0.005$, and $p = 0.030$, respectively)

PT IgG pertussis immunoglobulin G, *GMT* geometric mean titer, *PCR* polymerase chain reaction, *ELISA* enzyme-linked immunosorbent assay, *CI* confidence interval, *NTU* NovaTech units

9100–20,100)/100,000 per year in the population aged 12–20 years [32]. Consistent with these results, among 1032 children and adolescents in China between 2012 and 2013, the seroprevalence of anti-PT IgG ≥ 40 IU/ml varied from 4.48% in children aged 7–11 years to 11.76% in adolescents aged 12–18 years [33].

All Ages

A seroprevalence study in China was conducted between 2009 and 2017 and included a population of 3360 [35]. Seropositivity (PT IgG ≥ 16 EU/ml) was significantly lower in the age groups < 10 years, 20–29 years, and 30–-39 years compared with the other age groups evaluated [35]. Another study between 2010 and 2016, included 3058 randomly selected people aged 3–69 years (2010), and 826 people aged 20–39 years attending an annual medical examination (2015–2016). Comparing between the two periods, there was no difference in the seroprevalence of anti-PT IgG ≥ 40 IU/ml in the population aged 20–39 years (5.1% versus 4.0%) [38].

The incidence rate calculated for China based upon 113 confirmed cases (see Table 2 for definition), from 1089 possible cases, identified through active symptom surveillance from 2010 to 2012, was highest in infants and young children (aged < 6 years) [18]. The rate fell with age from 64.76/100,000 in children aged 7–-14 years to 10.58/100,000 in adolescents and adults aged 15–69 years. The authors noted that the annual incidence was 23.52/100,000 persons, which was 16.22 times higher that obtained via hospital reports for the same period ($p < 0.001$). The actual incidence in the population aged 15–69 years was significantly underestimated by hospitals, given that it was 43.08 times that of the hospital rate. Among cases aged < 15 years, 84.5% had been fully vaccinated. The misdiagnosis rate was as high as 94.69%, and only 5.31% of the confirmed pertussis cases were properly diagnosed as pertussis at the first medical visit [18].

A Chinese study of people aged 0–95 years, conducted in 2010, reported that of 1313 people, 117 (8.91%) were seropositive (PT IgG > 30 IU/mL), and the estimated incidence of recent infection was 9395/100,000 for those aged > 7 years [77]. The estimated incidence rate of recent infection peaked at 11,561/100,000 in those aged 41–50 years and at 11,428/100,000 in those aged 13–19 years [77]. Another population-based Chinese study between 2010 and 2012, included 1825 randomly selected people aged 0–76 years, and found an overall seropositivity (PT IgG > 30 IU/

mL) rate of 49.15%. By age group, the seropositivity rate was substantially lower in children aged 4–12 years than in other groups ($p < 0.001$) [39].

In an analysis of 1080 samples taken from a range of people aged 0–86 years in 2011, of 850 people aged ≥ 4 years, 56 (6.6%) had anti-PT IgG levels > 30 IU/mL, and 11 (1.3%) had anti PT-IgG levels of > 80 IU/ml [34]. The estimated age-specific incidence of infection (PT IgG ≥ 30 IU/mL) revealed a peak incidence in people aged 31–40 years, followed by those aged 41–60 years. A higher prevalence of anti-PT IgG levels > 30 IU/ml was observed in adults aged ≥ 21 years (42/502; 8.4%) than the population aged 4–20 years (14/348, 4.0%, $p < 0.05$), ranging from 6.48% in children aged < 2 years to 12.71% in adults aged 41–60 years [34].

Of 2047 residents of Beijing in 2012, including people aged up to 74 years, the highest seropositivity (PT IgG ≥ 28 IU/ml) rate was seen in infants aged < 1 year at 22.23% [78]. In people aged > 10 years, the seropositivity rate was 10.19–13.51% with no significant differences between the age groups. Those with anti-PT IgG ≥ 100 IU/ml were nearly all in the groups aged > 5 years, although there were none in the group aged 10–14 years [78].

In an all age group survey of 1080 people in 2015, the a rate of recent infection (PT IgG > 100 IU/mL) was 1.17% (11/944), which was highest in adults aged ≥ 20 years (2.23%), but with no significant differences between age groups [36]. The estimated pertussis infection rate was 7290/100,000, which was far higher than the nationally reported incidence of 1.29/100,000 in 2015. Peaks of estimated incidence of infection were found in children aged 7–-14 years (9971/100,000) and ≥ 20 years (13,898/100,000) [36].

Another large-scale survey in China in 2014 involving 2107 people aged up to 91 years showed that of 1707 people aged ≥ 3 years, 169 (9.90%) had evidence of a recent infection (PT IgG > 80 FDA-U/ml), with the highest proportion of recent infections among people aged ≥ 60 years, followed by those aged 11–-15 years and 16–25 years [31].

Burden

There were two studies of clinical burden in China, of which one included 48 laboratory-confirmed (mean age 42 years) cases in 2018 [59], and the other 26 laboratory-confirmed cases (aged 23–79 years) in 2009 [58]. Paroxysmal cough was a common symptom in both studies (47.8–54%), followed by vomiting (19–30.4%), yet whoop affected relatively few adults (2–21%). In the latter study the most common symptoms were nocturnal cough (69.2%) and persistent cough (68%), and the authors noted that in adults, paroxysmal cough and whooping was less common than in infants, and although the severity of coughing was generally lower in adults than that reported in infants, the symptoms are similar in all ages [58].

Taiwan

Vaccination with wP started in Taiwan in 1954, and this was replaced by aP in the 1980s [21]. The NIP in Taiwan currently includes, DTP at 2, 4, 6, and 18 months, and tetanus, diphtheria, and pertussis (Tdap) at 5 years [79]. Tdap is recommended for pregnant women and caregivers, but is not state funded. Coverage of DTP4 in Taiwan is greater than 90% [80]. Pertussis is a notifiable disease in Taiwan and confirmation tests are conducted at the Taiwan Center for Disease Control Laboratory [81].

In Taiwan, based on 668 cases reported to the Taiwanese Center for Disease Control and Prevention (CDC) from 2003 to 2017, the incidence rates of confirmed infection in infants accounted for the highest proportion of all cases (49.8%). The mean incidence rates were 0.46, 0.14, 0.39, 0.09, and 0.03 cases/100,000 population, respectively, in children aged > 4 years, 5–9 years, 10–14 years, 15–39 years, and > 40 years. Adolescents aged 10–14 years accounted for 12.4% [21]. A long-term survey of pertussis epidemiology in Taiwan between 1993 and 2004 among children aged ≤ 14 years (2452 reported cases) found that the highest morbidity was in infants aged < 1 year, and that there was a significant upward trend in the

incidence of pertussis in infants aged < 1 year and adolescents aged 10–14 years [22].

South Korea

DTP vaccination at 2, 4, 6, and 15–18 months was introduced to NIP in South Korea in 1982, and Tdap for children aged 11–12 years was added in 2012 [51, 82]. Tdap for pregnant women and adults in contact with neonates has been recommended since 2017 [83]. A single dose of Tdap is also recommended for adults, with a booster dose every 10 years [84].

Based on WHO estimates, coverage of DTP3 was about 98% in South Korea in 2019 [80]. Pertussis is a notifiable disease in Korea, and is monitored by the national sentinel surveillance system [85].

A large study in South Korea of 1192 healthy adolescents and adults in 2012 found that the pertussis seroprevalence (PT IgG > 24 EU/ml) was 41.4% [52]. The seroprevalence was not significantly different between the age groups, although the seroprevalence in individuals aged ≥ 51 years was significantly higher than in individuals aged < 51 years (46.5% versus 39.1%, $p = 0.017$) [52]. In South Korea in 2009–2011, among adolescents and adults ($n = 76$ laboratory-confirmed cases, unspecified cut-off value) divided into seven age groups (11–20 years, 21–30 years, 31–40 years, 41–-50 years, 51–60 years, 61–70 years, and ≥ 71 years), the group aged 11–20 years (26.3%) comprised the largest proportion of pertussis cases compared with the other six age groups; 6.6%, 15.8%, 13.2%, 15.8%, 17.1%, and 5.3%, respectively [53].

In a study in Korea of 398 HCWs aged 21–-67 years, including doctors, nurses, healthcare assistants, and non-clinical workers, overall, 121 (30.4%) had anti-PT IgG 5–40 IU/ml, and 3 had anti-PT IgG > 100 IU/ml, yet none had anti-PT IgG ≥ 125 IU/ml. By age group, those aged > 50 years had the highest mean antibody titer [51].

Burden

In a small outbreak study of nine cases identified at an elementary school (five aged < 8 years and four aged 9–10 years) in South Korea in 2017, one case (11%) required hospitalization [64]. All cases had cough, one (11%) had post-tussive vomiting, and one (11%) had fever. The overall pertussis attack rate in the school was 1%. Pertussis PCR-confirmed in eight cases and eight cases received antibiotics [64].

In a case-based surveillance study in South Korea between 2009 and 2011, among 504 probable cases defined by clinical criteria, paroxysmal cough (90.8%) and sputum (60.4%) were the most common symptoms. There were five PCR-confirmed cases, which had a median cough duration of 30 days (interquartile range [IQR] 18.0–50.0 days). Sputum, rhinorrhoea, and myalgia were less frequent, and dyspnoea was more frequent in the clinical cases compared with PCR-confirmed cases ($p = 0.037$, $p = 0.006$, $p = 0.005$, and $p = 0.030$, respectively) [62]. An abstract of a similar study in South Korea conducted between 2011 and 2012 included 578 adults (age, 44.4 ± 15.9 years) with a median cough duration of 15.0 days (IQR, 7.0–30.0 days). Thirty-five (6.1%) cases were PCR-confirmed, and sputum, rhonchi, and post-tussive vomiting were more common in patients with a positive PCR than those without ($p = 0.005$, $p = 0.007$, and $p = 0.036$, respectively) [28].

SOUTH AND SOUTHEAST ASIA

There were only four publications identified in South and Southeast Asian countries (Table 4).

Singapore

The NIP in Singapore includes DTP at 2, 4, 6, and 18 months, and a Tdap booster for children aged 10–11 years [86]. Tdap vaccination for pregnant women and adults in close contact with neonates has been recommended in Singapore since 2017 [87]. Tdap is also recommended for adults aged 19–64 years every 10 years, and for healthcare personnel who have direct patient contact [88]. Coverage of DTP3 in Singapore was greater than 98% in 2019 [80].

Table 4 Overview of studies of pertussis in children and adults in South and Southeast Asia

Country	Design, period	Age, *n*, sample type	Key findings
India [29]	Retrospective, population-based (outbreak in remote region) 6–15 August 2007	<6 years 72 suspected cases from population 2471	Attack rate 13% (age 3–60 months) 30 reported deaths 26 deaths aged <5 years; 15 infants
Thailand [54]	Prospective, population-based October 2010 to February 2011	15–85 years 76 patients with cough >2 weeks	Evidence of acute infection: 14 (18.4%), mean age 59 years, mean duration cough 34 days, had PCR-diagnosed: 13 cases
Singapore [44]	Prospective, population-based 2 days in August 2002	18–45 years 270 random sample 92: 18–25 years 89: 26–35 years 89: 36–45 years	261 (97%) positive serology: 96% in the 18 to 25 years cohort, 99% in the 26 to 35 years old cohort 96% in the 36 to 45 years old cohort
Singapore [43]	Prospective, hospital-based case surveillance August 2008 to July 2010	1–17 years 1200	Seroprevalence 60.8% (95% CI 58.0–63.5%)

CI confidence interval

In Singapore, 270 people with a median age of 30 years were enrolled in a study in 2002. Positive anti-PT IgG levels (unspecified cut-off value) were found in 97% of the population, and seropositivity was not associated with age, gender, or race. The authors noted that the seroprevalence in adults was much higher than the previously documented seroprevalence of around 50% in the adolescent age group in Singapore, and that this was most likely due to natural infection [44]. In a hospital-based study in Singapore, between 2008 and 2010, among 1200 children aged 1–7 years, the prevalence of anti-PT IgG > 22 IU/ml was 60.8% (95% CI 58.0–63.5%). This ranged from 64% in children aged 1–6 years to 55% in those aged 13–17 years [43].

India

DTP was added to the NIP in India in 1978, and the current schedule includes DTP at 6, 10, and 14 weeks, and at 15–18 months and at 5 years [89]. According to WHO, DTP3 coverage in India in 2019 was 89% [80].

There was one study in India and this reported pertussis cases during an outbreak in 2007 in the Sarli circle region, comprising 2471 people in 26 villages [29]. The overall attack rate, based on clinical suspicion, was 30% and none of the cases had been vaccinated. Among children aged < 6 years with suspected pertussis (all had cough of at least 2 weeks duration), common clinical features of the 72 case-patients identified in the medical camp were paroxysms of coughing (100%) and post-tussive vomiting (100%), yet inspiratory whooping was uncommon (1.3%).

Thailand

In Thailand, the NIP includes DTP at 2, 4, 6, months, and at 12–18 months and at 4 years [90]. According to WHO, DTP3 coverage in Thailand in 2019 was 97% [80].

Table 5 Overview of studies of pertussis in children and adults in multinational studies

Country	Design, period	Age, *n*, sample type	Test and serological cut-off value	Key findings
India, Thailand, Korea, China, Sri Lanka, and Japan [56]	Prospective, population-based July 2013 to June 2016	10–18 years 1894 convenience population sample	PT IgG ≥ 62.5 IU/ml	87 (4.8%) 73 (83.9%) had received ≥ 3 doses pertussis vaccine age < 6 years 30 had persistent cough during the past 6 months No significant difference in proportions with recent infection among age groups
Malaysia, Taiwan, and Thailand [55]	Prospective, outpatient-based, population-based June 2012 and May 2013	≥ 19 years 312 cough for 5–14 days	PT IgG ≥ 62.5 IU/ml PT IgG ≥ 100 IU/ml	16 (5.13%) 50–59 years (9.8%, 5/51, 95% CI 3.26–21.41) and 19–29 years (7.6%, 5/66, 95% CI 2.51–16.80) Most common in 19–29 years age group (3.0%, 2/66)

PT IgG pertussis immunoglobulin G

In a small study in Thailand between 2010 and 2011, among 76 patients with persistent cough of duration of at least 2 weeks, 14 (18.4%) had evidence of acute infection of pertussis (unspecified cut-off value) [54]. The mean age of pertussis cases was 59 years (range 28–-85 years) and the mean duration of cough was 34 days (range 14–120 days).

Pan-Asia

Two publications were identified which provided data from several countries (Table 5). The most recent multinational study assessed the seroprevalence of anti-PT IgG ≥ 62.5 IU/ml in six Asian countries between 2013 and 2016, including 1802 children/adolescents aged 10–-18 years [56]. The children had received five (India, Thailand, Taiwan, and Korea) or four (China, Sri Lanka, and Japan) doses of DTP before the age of 6 years. The rates of anti-PT IgG ≥ 62.5 IU/ml by age group were not significant: aged 10–12 years, 4.6%; aged 13–15 years, 5.6%, and 16–18 years, 4.1%. The main finding was that 1 in 20 had serologic evidence of recent infection regardless of vaccination background [56].

The other multinational study assessed the seroprevalence of pertussis in Malaysia, Taiwan and Thailand between 2012 and 2013, including adults aged ≥ 19 years [55]. A total of 312 adults were recruited from outpatient settings after consulting for chronic coughing for 5–-14 days, of which 5.13% had serological evidence of pertussis infection (PT IgG ≥ 62.5 IU/ml) within the previous 12 months, and 1.3% had evidence of active or recent infection (PT IgG ≥ 100 IU/ml). The most common symptom was paroxysmal coughing (75%) followed by nocturnal coughing (68.8%) and chest pain (62%), and a longer duration of cough, paroxysms, and breathlessness/chest pain were associated with being seropositive (PT IgG ≥ 10 IU/ml) versus seronegative [55].

DISCUSSION

Most of the studies identified for this review of pertussis in Asia were from Japan, China, South Korea, Taiwan, and Singapore. Despite high DTP4 or DTP5 coverage in these countries, pertussis is circulating, and the peak age of infection appears to be shifting away from infants and young children, and towards adolescents. However, information is unavailable in many LMICs in Asia, meaning that it is difficult to assess the circulation of pertussis and the effect of vaccination across the continent.

In the USA, Canada, Australia, and several European countries, high DTP4 coverage led to a dramatic decrease in the incidence of pertussis in infants and young children, yet despite high vaccine coverage, a resurgence of pertussis has been observed in many countries [91, 92]. Over the past decade there have been global epidemic outbreaks of pertussis every 3–5 years, and in 2012, there were epidemic outbreaks in Canada, Australia, France, the UK, Japan, and the USA [93–97]. In the USA in 2012, there were 48,277 notified cases of pertussis, up from 9771 a decade before, and the highest level since 1955 [98]. During epidemic outbreaks, the highest burden of severe cases is typically among unvaccinated or partly vaccinated infants [93–97]. For example, in 2012 in the UK, 14 infants aged < 3 months died, and in the USA, 14 infants aged < 12 months died [99, 100]. During an epidemic outbreak in California in 2010, there were about 9000 cases, 808 hospitalizations, and 10 infant deaths [101, 102]. Several high-income countries have introduced aP vaccination for pregnant women, including the USA in 2011, the UK in 2012, and Australia in 2012 [103–105]. Whereas more studies are needed to assess the effectiveness of maternal pertussis vaccination programs, studies from the UK, Australia, and the USA show that aP vaccine during or after pregnancy reduced the risk of pertussis in neonates [100, 101, 106]. The Global Pertussis Initiative (GPI) recommends vaccination during pregnancy as a primary prevention strategy, or vaccinating all individuals who have close contact with infants younger than 6 months [105, 107]. In Asia, Singapore, South Korea, and Hong Kong, aP vaccination for pregnant women is included in the NIP [83, 87, 108], and whereas it is recommended in Japan and Taiwan, it is not state funded [72, 79].

Globally, high DTP4 coverage has led to a change in the epidemiology of pertussis infection, characterised by a shift in the peak age of infection away from infants, and towards young children, and the introduction of a booster dose at school entry further increased the peak age of infection towards adolescents and adults [7, 8]. For example, after the introduction of a booster dose for children aged 5 years in Denmark in 2004, whereas cases decreased dramatically in the target population, the proportion of cases in adults aged ≥ 20 years increased from 14% to 43% [109]. Similarly, in the Netherlands, a preschool booster was introduced in 2005, which decreased infection rates in young children, yet pertussis notifications increased by 60% in adolescents aged 10–19 years, by 44% in adults aged 20–59 years, and by 68% in adults aged > 60 years [110]. On the basis of the these and other data, about 15 years ago, the GPI, the Consensus on Pertussis Booster Vaccine in Europe, and the US Advisory Committee on Immunization Practices (ACIP) recommended that adolescents and adults receive pertussis booster vaccination, and that Tdap vaccine should be given every 10 years to adults to improve community protection [7, 111, 112].

In the USA, the introduction Tdap vaccine for adolescents in 2005 resulted in a large decrease in pertussis cases among adolescents aged 11–18 years, and in Australia, after vaccinating high school children in 2008–2009, there was a decrease in pertussis cases in adolescents [113, 114]. Numerous countries, such as Australia, Canada, and France, include Tdap vaccine for adolescents in the NIP, yet the only countries to include 10-year booster doses for adults are Canada, Belgium, Germany, Italy, and Greece, and countries that include boosters specifically for elderly adults are Australia and the Czech Republic [115, 116].

In East Asian countries, including Japan and China, the NIPs currently include DTP4, and in South Korea, Hong Kong, and Taiwan the NIPs currently include DTP4, plus a DTP5 booster at

age 6 years in Hong Kong, age 7 years in South Korea, and age 5–7 years in Taiwan [31]. In Japan, there is a voluntary recommendation for booster doses at age > 7.5 years and 11–-12 years, yet this is not state funded [72]. Among ASEAN countries, Cambodia, Laos, Myanmar, and the Philippines provide DTP3, Indonesia, Malaysia, and Vietnam provide DTP4, and Brunei, Singapore, and Thailand provide DTP5 [17]. The NIP in India includes DTP5, and although the Indian Paediatric Society recommends Tdap vaccine for children aged 12–14 years, this is not state funded [89]. Tdap vaccine for adolescents is included in the NIPs of South Korea, Singapore, and Hong Kong [117, 118].

Similar to Europe and the USA, numerous population-based, active and passive surveillance studies from East Asian countries show that high DTP4 coverage has decreased the incidence of pertussis in infants, and has changed the incidence and immunity profiles of pertussis across the general population. In Japan, there have been several outbreaks of pertussis over the past two decades including schools, universities, hospitals, and workplaces, showing that pertussis infection persists with cyclical epidemics [16, 48, 60, 61, 119]. Similarly, the most recent study from the Taiwan CDC open database showed that between 2003–2008 and 2009–2015, there was a twofold increase in pertussis cases (unspecified serological cut-off value) in adolescents, with peaks of incidence in 2009, 2011, and 2014 [22]. School outbreaks in China show that pertussis is circulating in young children, advocating a booster dose for children of school entry age [19]. Moreover, studies in China suggest that pertussis may be underestimated, particularly in adolescents and adults who are reported to be the new high-risk populations [31, 34, 77].

A recent systematic literature review of pertussis in ASEAN countries reported that immunization schedules and vaccination coverage rates vary across the region and disease surveillance is suboptimal meaning that the true burden is unknown [17]. However, a study of adolescents in India, Thailand, Taiwan, Korea, China, Sri Lanka, and Japan showed that between 2013 and 2016, 1 in 20 individuals had serological evidence of recent infection (PT IgG $\geq$ 62.5 IU/ml), regardless of vaccination background [56]. Moreover, the countries have various economic status and infectious disease burdens, yet the anti-PT IgG levels among adolescents from different countries were similar. The seroprevalence of recent infection was estimated at 2.2–6.1%, and although this demonstrates that pertussis persists in adolescents in Asia, the authors noted that serological data were not available for most countries [56].

In high-income countries, with high vaccine coverage among infants and young children, the GPI recommends Tdap vaccine for adolescents, with a booster every 10 years, as well as aP vaccine for pregnant women [7]. The only countries in Asia to follow these recommendations are South Korea, Hong Kong, and Singapore, yet there are no available data evaluating the effect of vaccination on the target populations or general populations. In LMICs, the GPI recommends aiming for high DTP4 coverage, and states that pregnant women should receive aP vaccine as a priority [120]. However, the scarcity of data from numerous Asian countries means that the effect of vaccination, particularly in remote rural areas, is difficult to assess. Although the real extent of pertussis-related morbidity and mortality is not known in many countries, the burden of pertussis in LMICs should not be underestimated [120, 121].

The main limitation of this review is that it provides a narrative analysis; however, the variations in methods used to assess pertussis across the articles identified meant that a statistical comparison was not feasible. Furthermore, there was a lack of data from several countries, particularly in Southeast Asia, and for countries with robust national surveillance, there was a wide variation in reporting systems, with differing methods used for passive and active surveillance, clinical definitions, laboratory diagnostics, and antibody cut-off levels. A strength of the review was the systematic searches used to identify information about pertussis in older children and adults in Asia, whereas previous reviews have focussed on infants and young children.

CONCLUSIONS

In East Asia, including high-income countries such as Japan and South Korea, and higher middle-income nations including China and Taiwan, DTP4 coverage is high, yet passive and active surveillance show that pertussis is circulating in older children and adults [18–26, 28, 30–42, 45–53]. There are limited data from LMICs in Asia because surveillance is weak or absent, meaning that the true burden of pertussis among older populations is unknown.

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