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REVIEW

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

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ABSTRACT

Despite modern diphtheria-tetanus-pertussis (DTP) vaccines and high vaccine coverage, a resurgence of pertussis (whooping cough) has been observed globally. In North America and Europe, high vaccine coverage in children has led to a shift in the age-specific peak incidence of infection away from infants and towards older children and adolescents. However, much less is known about the prevalence of pertussis in older children and adults in the Middle East. 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 the Middle East. Studies identified for inclusion were reviewed narratively because a statistical comparison was not possible because of the mix of methodologies used. The results showed that surveillance data are weak or missing in most Middle Eastern countries, and among 24 epidemiological studies identified, most were from Iran (14), Israel (4), and Turkey (3), with single studies from the United Arab Emirates and Iraq. Despite various surveillance periods, clinical definitions, and antibody cut-off values used across the studies, the reported seroprevalence of pertussis antibodies suggested that adolescents and adults are commonly exposed to pertussis in the community and that vaccine-acquired immunity from childhood wanes. Few countries in the Middle East include a diphtheria-tetanus-acellular pertussis (Tdap) booster for adolescents on the national schedule. Israel was the only country with epidemiological data in a population that received Tdap, and the study showed that after the introduction of the adolescent booster dose, there was decrease in pertussis among children aged 5–14 years. To conclude, results from the Middle East suggest that in common with other regions, pertussis is widely circulating and that it might be shifting towards older age groups.

Keywords: Adolescents; Adults; Burden; Children; Epidemiology; Middle East; 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 the Middle East.

Thirty-two studies met the inclusion criteria.

The results showed that surveillance data are weak or missing in most Middle Eastern countries.

The reported seroprevalence of pertussis antibodies suggested that adolescents and adults are commonly exposed to pertussis in the community and that vaccine-acquired immunity from childhood wanes.

Results from the Middle East suggest that in common with other regions, pertussis is widely circulating and that it might be shifting towards older age groups.

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.14267744.

INTRODUCTION

Bordetella pertussis (whooping cough) was once a common childhood infection, but since mass vaccination that started in the 1950s, its incidence has diminished dramatically [1]. However, despite high diphtheria-tetanus-pertussis (DTP) vaccine coverage, a resurgence of pertussis has been observed in many countries, and over the past decade, there have been global epidemic outbreaks every 3–5 years [2, 3]. Between 2008 and 2016, for example, important epidemic outbreaks of pertussis have been reported in several countries including the US, Canada, Australia, Japan, the UK, Sweden, Poland, Malaysia, Argentina, Brazil, Colombia, and Mexico [4–10]. In the US in 2012, there were 48,277 notified cases of pertussis, up from 9771 a decade before, and the highest level since 1955 when there were 62,786 cases [11].

Several factors are implicated in the global resurgence of pertussis, including high vaccine coverage in young children, which shifted the age-specific peak toward older children, coupled with the waning of vaccine protection in adolescents [3, 12]. The duration of vaccine protection in epidemic and interepidemic periods is not established, yet numerous sero-surveillance studies show that anti-pertussis (PT) immunoglobulin G (IgG) levels decrease with time from vaccination, suggesting that immunity wanes in the years following the last dose of pertussis vaccine [13]. For high- and middle-income countries, the Global Pertussis Initiative currently recommends diphtheria-tetanus-acellular pertussis (Tdap) booster doses for adolescents and then every 10 years in adults to reduce transmission and to protect the community [13–15]. However, countries that have introduced a Tdap booster for adolescents report a shift in the age-specific peak incidence of infection towards the unvaccinated adult population, but few countries currently include adult booster doses on their national schedule [11, 16].

Similar to that observed in other regions, World Health Organization (WHO) estimates show that pertussis is circulating in the Middle East, with cyclical peaks, although national surveillance systems often focus on infants and young children, meaning that data are lacking in older populations [17]. In some high-income countries in the Middle East, the national immunisation programme (NIP) includes a four-dose DTP schedule in young children and DTaP booster doses for older children, yet in some countries, there are specific challenges for delivering vaccines and reducing the burden of infectious disease [18]. For example, the high number of refugees in Lebanon and Jordan

represents a substantial challenge to vaccine delivery, and conflicts in Iraq, Syria, and Yemen have resulted in a sharp decrease in DTP3 vaccine coverage [18]. There was a wide variation in notified pertussis cases reported to WHO in 2019 in the Middle East; for example, there were 9 cases in the United Arab Emirates (UAE), 78 in Lebanon, 242 in Iran, and 302 in Syria, whereas no data were available from Yemen [17]. Moreover, incidence rate estimates based on national surveillance reports likely underestimate the true burden of pertussis in young children in the Middle East, and the importance of older children and adults in the transmission dynamic in the region is unclear [19].

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 the Middle East.

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. 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 Europe, Asia, and Africa are provided as parallel publications. The search results for the global analysis are shown in Supplement 3. This article provides the results of articles identified with relevant data from countries in the Middle East.

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 8 surveillance studies and 16 sero-surveillance studies of pertussis in the Middle East, including Iran [20–33], Israel [34–36], Iraq [37], United Arab Emirates (UAE) [38], and Turkey [39–41]. An overview of epidemiological/sero-epidemiological studies is shown in Table 1 for Iran and in Table 2 for the other countries with available data. There were five

Table 1 Overview of epidemiological studies of pertussis in Iran

Country	Design, period	Age, *N*, sample type	Serological cut-off value	Results
Iran [27]	Prospective, population based, case surveillance 2015 to 2016	Adults 88 parturient mother-neonate pairs	Mother PT IgG Cut-off not stated	33% negative; 13.6% equivocal; 53.4% positive
Iran [31]	Prospective, population based, case surveillance March 2015 to June 2016	0–70 years 184 suspected cases	PT IgG > 24 IU/ml	62.16% (69/111) Age: cases (% of 12–70 years group) 12–18 years: 13 (18.8%) 19–30 years: 15 (21.7%) 31–40 years: 26 (37.7%) 41–50 years: 7 (10.2%) 51–70 years: 8 (11.6)
Iran [23]	Prospective, longitudinal, population based, surveillance 2011 to 2013	Young children and adolescents 3629 Suspected cases	Cut-off not stated	239 (6.6%) laboratory-confirmed 3390 (934%) cases clinical diagnosis Winter: Aged < 2 months: average 32.9 cases Aged 2–11 months: average 41.8 cases Summer: Aged 1–5 years: average 13.7 cases Aged 6–10 years: average 11.7 cases Aged > 10 years: average 18.9 cases

Table 1 continued

Country	Design, period	Age, *N*, sample type	Serological cut-off value	Results
Iran [28]	Prospective, population based, active surveillance 2007	17–38 years 1617 university students	PT IgG > 94 U/ml PT IgG > 100 U/ml	31.6% Age: number with (% of overall population) < 20 years: 1079 (66.9%) 20–24 years: 470 (29.1%) 25–29 years: 61 (3.8%) > 30 years: 4 (0.2%)
Iran [24]	Prospective, population based, active surveillance October 2010 to June 2011	6–17 years 640 school children	PT IgG > 24 U/ml	301 (47.0%) Age: number seropositive (% of age group) 6–11 years: 132 (47.1%) 12–14 years: 92 (51.4%) 15–17 years: 77 (42.5%)
Iran [22]	Retrospective, population based, passive surveillance 2008 to 2011	All ages 518 suspected cases	Clinical (probable) or laboratory confirmed cases Cut-off not stated	43 confirmed-cases Incidence 4.92/100,000 Age, probable cases (proportion of overall cases) 0–2 months: 71 (13.7%) 2–12 months: 125 (42%) 1–4 years: 152 (29.3%) 5–9 years: 54 (10.4%) 10–14 years: 34 (7.3%) 15–25 years: 78 (15%)
Iran [26]	Prospective, population based, hospital based, case surveillance 2013	Adults 40 suspected cases	PT IgG Cut-off not stated	15%
Iran [70]	Prospective, population based, health facility based October 2011 to March 2012	Adults 288 pregnant women	PT IgG > 24 IU/ml	126 (43.8%) in the second trimester 103 (35.8%)

Table 1 continued

Country	Design, period	Age, *N*, sample type	Serological cut-off value	Results
Iran [20, 21]	Prospective, school based, case surveillance September 2007 to November 2008	6–14 years 6601 coughing for 2 weeks	PCR-confirmed Cut-off not stated	21/6,601 (6.40%) Incidence B pertussis 318/100,000 Incidence B parapertussis: 2/100,000
Iran [29]	Prospective, population based, community based March to December 2008	1–35 years 580 random sample	PCR-confirmed Cut-off not stated	Aged 1–2.9 years: 72% seropositivity (mean PT IgG: 63.50 U/ml) Aged 3–6.9 years: 71% seropositivity (mean PT IgG: 73.90 U/ml)
Iran [30]	Prospective, population based 2009	6–20 years 833 random sample	PT IgG > 24 U/ml	45.5% (95% CI: 42.1–48.9) Aged 6.0–10.9 years: 39.1% Aged 11.0–15.9 years: 45.8% Aged 16.0–20.9 years: 57.4% Seropositivity rates between age groups $p < 0.001$ Mean: 43.3 ± 47.8 U/ml
Iran [25]	Prospective, active surveillance Publication date: 2011	18–21 years 424 military recruits	PT IgG > 20 U/ml	Positive history of whooping cough: 48 (11.3%) Seropositivity (70.0%)
Iran [32]	Prospective, population based March and June 2007	Adults 163 asymptomatic medical students	PT IgG > 24 IU/ml	47.6% (95% CI: 68.1–75.3) PT IgG mean 71.7 U/ml

PT pertussis toxin; *IgG*, immunoglobulin G; *IgA* immunoglobulin A

clinical burden studies, including three in Israel [34, 42, 43] and two in Iran [21, 31] (Table 3). There were three studies with information on pertussis-related deaths, including one from Israel [44] and two in Iran [45, 46].

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

Table 2 Overview of epidemiological studies of pertussis in Iraq, UEA, Israel, and Turkey

Country	Design, period	Age, *N*, sample type	Serological cut-off value	Results
Iraq [37]	Prospective, case surveillance (outbreak) June to December 1996	All ages 133 with clinical diagnosis/laboratory diagnosis	PCR-confirmed Cut-off not stated	B pertussis and B parapertussis: 133 cases Age (n): proportion of total population < 1 year (35): 26.3% 1–4 years (18): 13.5% 5–9 years (0): 0% 10–19 years (25): 18.8% 20–29 years (25): 18.8% ≥ 30 years (30): 22.6%
UEA [38]	Prospective, population based, outpatient based July 2014 and September 2015	23 months to 6 years 227 random sample	Seropositive: > 11 NTU	39.2% (95% CI 32.8–45.8)
Israel [53]	Prospective, active surveillance 1 January and 31 December 1993	17–18 years 533 military recruits	PT IgG > 70 U/ml PT IgG < 60 U/ml PT IgG 60–70 U/ml	58.6% positive 35.4% negative 6% borderline
Israel [34]	Prospective, active surveillance (outbreak day care centre) December 2005 to January 2006	3.5–5.0 years 31 children	PCR-confirmed Cut-off not stated	56% laboratory-confirmed 6/31 (19%) PCR-confirmed pertussis 4 cases were in unvaccinated children
Israel [35]	Retrospective, outbreak surveillance April to June 1987	All ages 78 clinical cases	Laboratory confirmed Cut-off not stated	Attack rate: Aged 4–11 years, 36.1% (11% of all cases) Aged > 20 years, 19.2%

Table 2 continued

Country	Design, period	Age, *N*, sample type	Serological cut-off value	Results
Israel [36]	Retrospective, population based, passive surveillance 1998 to 2009	All ages 1524 notified cases	Laboratory-confirmed Cut-off not stated	12.5% aged < 1 year (incidence 72.3/100,000) 1134 (74.4%) cases aged < 20 years Age, distribution of cases 1–4 years, 11% 5–9 years, 18% 10–14 years, 24.1% 15–19 years, 8.9%
Turkey [40]	Prospective, population based, passive surveillance 2014 (publication date)	6 months to ≥ 60 years 400 random sample	PT IgG < 10 EU/ml PT IgG 10–100 EU/ml PT IgG ≥ 100 EU/ml PT IgG ≥ 100 EU/ml	8.5% 68.2% 23.3% lowest (18.9%) aged 5–6 years highest (34.3%) aged 15–19 years
Turkey [41]	Prospective, population based, case surveillance February to December 2010	6–8 years (n = 150), 9–11 years (n = 90), 12–14 years (n = 67) 158 admitted to hospital with paroxysmal cough	PCR-confirmed Cut-off not stated	Age, % 0–12 months, 41% 7–12 years, 44% 13–18 years 40% > 1–6 years 34%
Turkey [39]	Prospective, case surveillance November 2004	6–14 years 1859 school children with cough ≥ 2 weeks	PT IgG ≥ 100 EU/ml PT IgG ≥ 100 EU/ml	49 (15.3%) Age, % 6–8 years, 14.7% 9–11 years, 23.3% 12–14 years, 8.9% GMTs no significantly difference between age groups

UEA United Arab Emirates; *NTU* NovaTec units; *CI* confidence interval; *PT* pertussis toxin; *IgG* immunoglobulin G

Table 3 Overview of studies reporting pertussis clinical burden in older children and adults

Country	Design, period	Age, *N*, sample type	Key findings
Iran [31]	Prospective, population based, case surveillance March 2015 to June 2016	0–11 years (n = 11) 12–18 years (n = 13) $\geq$ 19 years (n = 59) 184 suspected cases	Four most frequent symptoms: Aged 0–11 years: paroxysmal cough (100%); whoop (63.64%), vomiting (45.45%), hospitalisation (45.45%) Aged 12–18 years: paroxysmal cough (100%), gagging (38.46%), vomiting (23.08), dyspnoea (15.38%) Adults $\geq$ 19 years: paroxysmal cough (94.91%), gagging (30.51%), dyspnoea (27.12%), vomiting (11.86%)
Iran [21]	Prospective, population based, active surveillance September 2007 to November 2008	6–14 years 6601 random sample school children	328 with cough $\geq$ 2 weeks: n = 21 with laboratory-confirmed pertussis: duration of cough: 48.6 $\pm$ 74.4 days n = 307 without laboratory-confirmed pertussis: duration cough: 29.9 $\pm$ 42.2 days Symptom: no. with confirmed pertussis (%) and without confirmed pertussis (%); p value Whoop: 15 (71.4%) and 167 (54.4%); 0.13 Paroxysms: 17 (80.9%) and 177 (57.6%); 0.04 Post-tussive vomiting: 13 (61.9%) and 60 (19.5%); 0.001 WHO clinical criteria: 20 (95.2%) and 261 (85.0%); 0.33
Israel [34]	Prospective, case surveillance (outbreak day care centre) December 2005 to January 2006	3.5–5.0 years 31 children	6 confirmed cases: 4 unvaccinated: n = 1 paroxysmal cough 1–2 weeks n = 1 paroxysmal cough 2–3 weeks, whoop n = 1 paroxysmal cough 3–4 weeks n = 1 paroxysmal cough 3–4 weeks, whoop 2 vaccinated: n = 1 paroxysmal cough 0–1 week, whoop n = 1 paroxysmal cough 2–3 weeks, whoop
Israel [43]	Retrospective, case surveillance (outbreak) March to May 2001	Adults 107 military personnel	Cough $\geq$ 30 days: 21% plus PCR-confirmed 9.5% (PT IgG > 11 EU) *N* with cough: proportion PT IgG seropositive 48 no cough: 6% 11 cough < 30 days: 7% 30 cough $\geq$ 30 days: 37%

Table 3 continued

Country	Design, period	Age, *N*, sample type	Key findings
Israel [42]	Retrospective, population based, passive surveillance 1986 and 1991	5–10 years (n = 70) 11–14 years (n = 16) 15–30 years (n = 9) 95 notified cases	100% prolonged cough (mean 4.6 ± 3.6 weeks) 93% dry cough 22% paroxysmal cough 13% vomiting 6% classic whoop 13% temperature > 37.5 °C n = 5 visited emergency department for severe cough and dyspnoea n = 2 hospitalised for severe pneumonia

PT pertussis toxin; *IgG* immunoglobulin G; *WHO* World Health Organization

and interepidemic. The differences between studies meant that it was not possible to perform any meaningful statistical analysis combining the studies for any parameter, so a narrative review was performed.

Iran

Whole-cell pertussis vaccine has been used in Iran since the 1950s and continued to be used after the Expanded Program of Immunization (EPI) was launched in 1984 [47]. From the late 1980s, whole-cell pertuss (wP) coverage has been high in Iran among infants and school children, and the National Immunisation Programme (NIP) includes DTwP at 2, 4, 6, 18 months and 6 years, but does not include booster doses for adolescents [47]. Based on WHO data, the coverage of DTP3 among children aged < 1 year was 99% in 2019 [48].

Epidemiology

Articles identified for Iran provided epidemiological data from 2007 to 2016, with active surveillance in schools, universities, military facilities, and hospitals as well as passive surveillance in the general population (Table 1).

A sero-epidemiological survey conducted in 2007 among Iranian university students pursuing a medical degree found seropositivity [IgG PT > 24 international units (IU)/ml] rates of 33% in those aged < 19 years, 51% in those aged 19–21 years, and 45% in those aged > 21 years [32]. In Iran in 2007, an active surveillance survey of 1617 university students aged 17–38 years with persistent cough showed that 511 (31.6%) had anti-PT IgG > 94 U/ml. By age, the rates of anti-PT IgG levels > 100 U/ml were: < 20 years, 20–24 years, 25–29 years, and > 30 years: 1079 (66.9%), 470 (29.1%), 61 (3.8%), and 4 (0.2%), respectively [28].

In a case surveillance study of Iranian school children aged 6–14 years presenting with cough of ≥ 2 weeks duration between 2007 and 2008, 3.2% were aged 6–8 years, 1.2% aged 9–11 years, and 11% aged 12–14 years. The frequency of polymerase chain reaction (PCR)-positive cases increased significantly with age, with the highest rates observed in children aged 14 years (13.3%), 13 years (10.9%), and 12 years (10.0%), with lower rates in those aged 7 years (5.3%), 8 years (2.8%), and 9 years (4.8%), and no cases in those aged 6, 10, and 11 years [20, 21]. In 2008, among 595 healthy individuals aged

1–35 years seroprevalence rates varied between five different age groups. In children aged 1–2.9 and 3–6.9 years the rate of seropositivity was 72% (mean PT IgG: 63.50 U/ml) and 71% (mean PT IgG: 73.90 U/ml), respectively [29]. In another serosurvey in 2009, plasma samples of 833 children aged 6–20 years were assessed for pertussis infection (PT IgG > 24 IU/ml). The overall prevalence of pertussis antibodies was 45.5% (95% CI 42.1–48.9%), and seropositivity rates were significantly different between three age groups ($p < 0.001$): aged 6.0–10.9 years, 39.1%; aged 11.0–15.9 years, 45.8%; aged 16.0–20.9 years, 57.4% [30].

There were 518 probable pertussis cases reported to Mazandaran Center for Diseases Control and Prevention in Iran between 2008 and 2011, of which 43 (8.3%) were culture confirmed [22]. The highest number of cases in a year was 2008 with 235 probable cases, with 111 cases in 2009, 67 in 2010, and 105 in 2011. The mean incidence rate for 2008–2011 was 4.92/100,000. By age, the proportion of probable cases was: aged < 1 year, 37.7%; aged 1–-4 years, 29.3%; aged 5–9 years, 10.4%; aged 10–14 years, 34 (7.3%); aged 15–25 years, 78 (15%). A serosurvey of pertussis in 2010–2011 showed that among 640 children and adolescents aged 6–17 years, anti-PT IgG levels > 24 IU/ml were detected in 301 (47.0%), with a similar proportion of each age group affected: 6–11 years, 47.1%; 12–14 years, 51.4%; 15–17 years, 42.5% [24].

In Iran, a study of 424 military recruits aged 18–21 years in 2010 showed that 48 (11.3%) had a positive history of whooping cough [25]. A total of 167 (39.4%) had anti-PT IgG levels < 20 U/ml and 86 (20.3%) had anti-PT IgG levels > 80 U/ml. The authors concluded that military conscripts in Tehran garrisons were not serologically immune to pertussis and also confirmed the low awareness about vaccination and medical history related to pertussis infection in this subgroup [25].

In a hospital-based case surveillance study in Iran in 2012, among 42 adults with suspected pertussis, characterised by prolonged cough, 15% had PCR-confirmed pertussis [26]. Among 288 pregnant women admitted to hospital in Iran in 2011–2012, 35% were positive for pertussis infection (PT IgG > 24 IU/ml) [33]. In another study in Iran in 2016–2017, of 88 mothers with a mean age of 29 years, 4.5% had evidence of pertussis infection (PT IgG level unspecified); overall, 81% were vaccinated in childhood suggesting that vaccine-acquired immunity had waned over time [27].

A longitudinal study in Iran between 2011 and 2013 assessed seasonal rather than age variations among reported pertussis cases and found that the highest seasonal incidences of clinical pertussis were observed among children < 11 months in winter, yet in summer, the seasonal incidence was an average of 11.7 cases in children aged 6–10 years and 18.9 cases in children aged > 10 years (average 18.9 cases). None of the differences were statistically significant ($p > 0.05$) [23].

In a population-based case surveillance study in Iran between 2015 and 2016, there were 184 suspected cases among people aged 0–70 years (mean age 20 ± 19 years); the overall enzyme-linked immunosorbent assay (ELISA)-confirmed seropositivity (PT IgG > 24 IU/ml) rate was 62.16% (69/111) [31]. The highest rates of confirmed pertussis were among adults aged 31–-40 years. The number of cases by age was: 12–18 years, 13 cases; 19–30 years, 15 cases; 31–40 years, 26 cases; 41–50 years, 7 cases; 51–-70 years, 8 cases. There were 73 cases in children aged < 12 years, of which 11 were PCR-confirmed.

Mortality

An analysis in Iran that was part of the Global Burden of Disease study calculated mortality rates based on a systematic literature review and extraction of data and showed that in 2010 the overall pertussis-related mortality rate was 0.0264/100,000 [46]. By age group in Iran in 2010, the mortality rates (per 100,000) were 0.3025 in children aged < 5 years, 0.0031 in children aged 5–14 years, 0.0009 in those aged 15–49 years, and 0.0027 in adults aged 50–69 years.

Burden of Disease

Burden of disease studies are shown in Table 3. In a study of pertussis symptoms in Iran between 2015 and 2016, among 83 patients aged 0–70 years with laboratory-confirmed pertussis, overall, 100% had paroxysmal cough, 63.6% had inspiratory whoop, and 45.5% had post-tussive vomiting [31]. There were five (45.4%) cases requiring hospitalisation, of which all were aged < 1 year. Among 13 cases in adolescents aged 12–18 years, all had paroxysmal cough and 38.5% had post-tussive gagging. In adults, the most common symptoms after prolonged/proximal cough were gagging after a cough (30.5%) and dyspnoea (27.1%). There were no pertussis-related deaths observed [31].

Pertussis circulation and symptoms were assessed among school children in Tehran between 2007 and 2008, and among 6601 children aged 6–14 years [21]. A total of 328 had a cough of ≥ 2 weeks duration, of which pertussis infection was laboratory-confirmed in 21 children. The mean duration (standard deviation) in children with confirmed pertussis was 48.6 (74.4) days and in those without laboratory-confirmed pertussis was 29.9 (42.2) days. Among children with and without confirmed pertussis, 71.4% and 54.4%, respectively, reported whoop. There was a significant difference between children with and without laboratory-confirmed pertussis for paroxysms at 80.9% versus 57.6%, respectively ($p = 0.04$), and for post-tussive vomiting at 61.9% versus 19.5% ($p = 0.001$) [21].

Iraq

The EPI was established in Iraq in 1985, yet successive conflicts and economic sanctions have led to shortages in vaccines and poor access to basic health services [49]. Based on Department of Health Statistics during the years for Iraq from 2000 to 2016, there were peaks in the number of pertussis cases reported in 2004 and 2009, which are reported to have occurred after a decrease in vaccine coverage in the preceding years. Between 2008 and 2016, there was a mean of 2267 cases annually [49]. From 2012, the NIP in Iraq has included DTP at 2, 3, 6, and 18 months and at 4–6 years [50]. Based on WHO data, the coverage of DTP3 among children aged < 1 year was 84% in 2019 [48].

Epidemiology

There was only one epidemiological study providing information on pertussis in adults, which was an active surveillance study during a pertussis outbreak in Basra in 1996. Among 133 cases that were clinically diagnosed and laboratory confirmed using bacterial isolation, the highest incidence was among infants aged < 1 year (26.3%) followed by adults aged ≥ 30 years (22.6%), whereas there were no cases in children aged 5–9 years. Overall, 37% of cases were aged > 10 years. A total of 16 (45.7%) aged < 1 year were admitted to hospital, and there were no hospitalisations in the other aged groups [37].

Israel

Pertussis vaccination was included in the NIP in Israel in 1957, and high coverage is reported to have resulted in a stable annual incidence rate of 1–2/100,000, with outbreaks of modest magnitude every 3–4 years [51]. The NIP in Israel includes DTaP at 2, 4, 6, and 12 months, at 7–8 years (since 2005), and at 13–14 years (since 2011) [44, 52]. Based on WHO data, the coverage of DTP3 among children aged < 1 year was 98% in 2019 [48].

Epidemiology

Articles identified for review included active surveillance of children, military personnel, and national surveillance of the general population, with data available from 1987 to 2016 (Table 2).

Active surveillance during an outbreak in an Israeli kibbutz in 1987 affected 78 people (64% laboratory-confirmed) among a total of 964. The highest attack rate (36.1%) was in the group aged 4–11 years, and this age-group accounted for 71.8% of all cases, although comprising only 16% of the kibbutz population. The vaccination rate in this age group was 100% compared with 97.4% for all cases. The attack rate was 19.2% in people aged > 20 years, an age-group comprising 60% the population [35].

An Israeli study of 533 military recruits aged 17–18 years in 1993 reported that, of the sera tested, 58.6% were seropositive for pertussis (PT IgG > 70 IU/ml), 35.4% were negative (PT IgG < 60 IU/ml), and 6% were borderline (PT IgG 60–70 IU/ml) [53].

An evaluation of the vaccination programme in Israel found that 74.4% (1134/1524) of notified cases between 1998 and 2009 were in people aged < 20 years [36]. Infants aged < 1 year had the highest average incidence rate at 72.3/100,000 (12.5% of cases), among which 84.3% were aged < 6 months. The case distribution among ages 1–4 years, 5–9 years, 10–14 years, and 15–19 years was 11%, 18%, 24.1%, and 8.9%, respectively [36].

In a study of 31 children aged 2.5–5.5 years during an outbreak at an Israeli day care centre between 2005 and 2006, 6 (19%) children had PCR-confirmed pertussis, of which 4 had not been vaccinated. Of the two cases in vaccinated children, one was asymptomatic and the other was mild. The incidence of pertussis was significantly lower in the vaccinated group (2/27) than in the unvaccinated group (4/4) ($p = 0.000$) [34].

Mortality

In a national surveillance study in Israel, between 1999 and 2016, there were 19 pertussis-related deaths, and all were among infants (case fatality rate, 0.7%) [44].

Clinical Burden

Clinical burden studies are shown in Table 3. In 2001, there was a pertussis outbreak among Israeli soldiers, with an overall attack rate of 9.5% based on clinical signs with laboratory confirmation [43]. Among asymptomatic and previously symptomatic soldiers, 20% were PCR positive for pertussis. Symptoms were assessed among 107 soldiers, divided into three groups by the presence and duration of cough: persistent cough of ≥ 30 days ($n = 34$), short duration cough of < 30 days ($n = 18$), and no cough ($n = 55$). Seropositivity rates for anti-PT immunoglobulin A (IgA), IgG, and immunoglobulin M (IgM) differed significantly among the three groups. In the groups with cough, for those with cough for < 30 days and those with cough for ≥ 30 days, respectively, the frequency of symptoms was paroxysmal cough, 33% and 91%; whooping, 6% and 55%; post-tussive vomiting, 0% and 29%; rhinorrhoea, 61% and 77%; and sputum production 67% and 91% [43].

In December 2005/January 2006, there was a pertussis outbreak in Israel at a day care centre attended by 32 children aged 3.0–5.5 years and 3 staff members aged 26–48 years [34]. There were six confirmed cases of pertussis among children, of which four were unvaccinated. Among the unvaccinated cases, one had a paroxysmal cough for 2 weeks, one had paroxysmal cough for 3 weeks with whoop, and two had paroxysmal cough for 4 weeks, one with and one without whoop. In the two vaccinated cases, the duration of paroxysmal cough was 1 week and 3 weeks, both with whoop.

A retrospective analysis of 95 Israeli cases, who had all been previously vaccinated, but had developed laboratory-confirmed pertussis between 1986 and 1991, reported that there was a relatively low level of symptoms [42]. All patients had a prolonged cough of mean duration 4.6 ± 3.6 weeks, 93% had dry cough, 22% had paroxysmal cough, 13% had vomiting, 6% had whoop, and two patients were hospitalised for severe pneumonia. The mean duration between onset of symptoms and diagnosis of pertussis was 23 ± 15 days, and incorrect diagnoses included *Mycoplasma pneumoniae* infection (17%), sinusitis (7%), upper respiratory tract infection (4%), asthma (4%), laryngitis (3%), and suspected cystic fibrosis (1%). The initial diagnosis was pertussis in 46% of cases most of which were diagnosed in a kibbutz during an outbreak [42].

Turkey

The NIP in Turkey includes DTwP at 2, 3, 4, and 16–24 months, with no further booster doses of wP [54]. Based on WHO data, the coverage of DTP3 among children aged < 1 year was 99% in 2019 [48].

Epidemiology

Studies from Turkey are shown in Table 2. In 2004 in Turkey, the parents of 1698 school children aged 6–14 years answered a questionnaire that included a question on the presence or duration of cough [39]. Three hundred eighty-three (22.6%) of the school children had had a cough for ≥ 2 week duration, and 307 (80.2%), whose parents gave consent, were included in the study. Of these, 51 children (16.6%) had evidence of acute recent pertussis infection [39]. By age, recent infection (PT IgG ≥ 100.1–200 EU/ml at first serum sample) was reported by 7.4% of children aged 6–8 years (N = 150), 11.1% of children aged 9–11 years (N = 90), and 8.5% of children aged 12–14 years (N = 67).

In another study in Turkey in 2010, among 158 children aged 9–14 years admitted to hospital with paroxysmal cough or prolonged cough, 11% were aged 9–11 years, 7.4% were aged 6–8 years, and 7.5% were aged 12–14 years. PCR-confirmed pertussis ranged from 34 to 44% across age groups [41]. In another study in 2014, among 400 healthy people (age 6 months to ≥ 60 years), the prevalence of recent/acute infection (PT IgG ≥ 100 IU/ml) was lowest among children aged 5–6 years (18.9%) and was highest among adolescents aged 15–19 years (34.3%). Overall, 8.5% had anti-PT IgG < 10 European units (EU)/ml, 68.2% had anti-PT IgG 10–100 EU/ml, and 23.3% had anti-PT IgG ≥ 100 EU/ml [40].

UEA

The mandatory childhood vaccination schedule in the UEA is DTaP at 2 and 4 months, DTP at 6 months, DTaP at 18 months and at school entry, and Tdap at high school entry [55]. One study identified from the UEA was a population-based study of children aged 23 months to 6 years attending the Well-Child Care Programme of the Ambulatory Healthcare Services in Al-Ain between 2014 and 2015 [38]. The study assessed several vaccine-preventable diseases. The seroprevalence rates varied among the diseases studied, ranging from 39.2% for pertussis (> 11 NovaTech units) to 98.3% for rubella.

DISCUSSION

The aim of this systematic literature review was to evaluate the incidence, burden, and mortality of pertussis in older children and adults in the Middle East. Of 24 epidemiological studies identified for review, 14 were from Iran, 4 were from Israel, and 3 were from Turkey, and there was 1 study each from UAE and Iraq.

In Iran, high vaccination coverage with wP has dramatically reduced the incidence of pertussis, and between 1979 and 2011, the incidence decreased from 40/100,000 to 1.12/100,000 [56]. Despite this, pertussis persists in Iran, with cyclical epidemics every 3–5 years as observed in many other countries. Based on WHO reports in Iran there were 242 cases in 2019, 335 cases in 2018, 14 cases in 2017, 116 cases in 2016, and 145 cases in 2015, meaning that in 3 of the past five years, pertussis was the most frequently reported vaccine-preventable disease [17].

The NIP in Iran includes wP at 2, 4, and 6 months and a wP booster at 18 months, and unlike most middle-income countries, the schedule also includes a booster dose at 5–-6 years [47]. However, after the introduction of a pre-school booster in several high-income countries, there was a shift in the epidemiology of pertussis infection, characterised by an increase in infections in older children and adults [57–60]. As reported globally, after the introduction of DTP5 schedules, several articles identified for review reported that pertussis is widespread among Iranian adolescents and young adults [24, 28, 30, 32]. In Iran in 2010 and 2011, a serosurvey showed that among children and adolescents aged 6–17 years, nearly half had anti-PT IgG levels of > 24 IU/ml, with a similar proportion affected in the 6–-11 year (47.1%), 12–14 year (51.4%), and 15–-17 year (42.5%) age groups [24]. The authors noted that the pertussis antibody levels were not, as expected, lower in the young children versus adolescents, yet were similar, suggesting the presence of natural infection in the

community, which may have increased the antibody levels in adolescents [24]. Active surveillance of Iranian university students aged 17–38 years with persistent cough in 2007 showed that the incidence of acute infection was 31.6% (PT IgG > 94 U/ml), and the seroprevalence of anti-PT IgG was high at various cut-off values: 40, 80, and 100 U/ml and 55.4%, 37.7%, and 28.4%, respectively. Moreover, the students were recruited to the study on the first day of university and therefore before entering crowded lecture halls and dormitories, suggesting that pertussis was circulating in the community and that vaccine-acquired immunity had waned [28].

A recent serosurvey study that was published after the review search period assessed children and adolescents aged 3–15 years in Tehran between December 2016 and February 2017. The seroprevalence of anti-PT IgG showed that *B. pertussis* was circulating, despite high coverage of childhood pertussis vaccination and the pre-school booster [61]. Among serum samples from 1010 children and adolescents, the seropositivity rate (PT IgG > 40 IU/ml) was significantly higher among children who received their first booster dose 5–6 years previous to the study compared with those who had received it within 1–2 years (30.4% versus 2.4%, respectively). In children who had received the second booster dose, seropositivity rates in children receiving it within 1 years and 1–2 years were 27.7% and 32.5%, respectively, and rates were significantly lower in children receiving it within 2–3 years (11.1%). The authors suggest that vaccine-acquired immunity after the first booster dose at 18 months had waned within about 2 years and that a second booster dose in children aged 5–6 years improves longer term antibody persistence [61].

Nearly 2 decades ago, the Global Pertussis Initiative recommended expanding vaccination strategies to include a booster dose for adolescents, and this, as well as the availability of acellular pertussis vaccines, led to numerous countries adding a pertussis booster dose for adults and/or adolescents to their immunisation schedule [13]. Countries in the Middle East with pertussis booster doses for adolescents on the national schedule include Israel, Lebanon, UAE, and Saudi Arabia, although Israel was the only country with available epidemiological data in a population that had received a Tdap booster [36, 62–64].

The NIP in Israel currently includes DTaP at 2, 4, 6, and 12 months and a Tdap booster at age 7–8 years (since 2005) and at age 13–14 years (since 2011) [44, 52]. In a study between 1998 and 2009, the incidence of notified pertussis cases in Israel was highest among infants aged < 1 year (72.3/100,000), and the incidence (per 100,000) of pertussis in the general population was 2.6 in 1990, 10 in 2000, 28.8 in 2006, and 15.7 in 2009 [36]. The number of notified cases among children aged 5–9 years decreased by 61.5% between 2006 and 2009 and by 73.9% among children aged 10–14 years. Of note was that in children aged 5–14 years, there was a 96.6% increase in cases between 1998 and 2006 and a 68.4% decrease in cases between 2006 and 2009. Whereas the decrease in pertussis among older children and adolescents was suggested to be associated with the introduction of the Tdap booster, the changes observed were also likely due to cyclical fluctuations in the circulation of pertussis [36]. Furthermore, during an outbreak among a highly vaccinated population on an Israeli kibbutz in 1987, of a population of 964, pertussis affected 78 people, among which the attack rate was highest in children aged 4–-11 years at 36.1%; among adults aged > 20 years, the attack rate was 19.2% [35].

The incidence and clinical burden of pertussis is underestimated globally partly due to the increased prevalence of infections among adolescents and adults and also due to misdiagnosis and low clinical suspicion among older groups with mild or atypical symptoms [13, 19]. The initial symptoms of pertussis are sore throat, sneezing, and an irritating cough, which are similar to other acute respiratory infections. In an assessment of 95 notified patients aged 5–30 years in Israel in 1986–1991, the mean time from the onset of symptoms to pertussis diagnosis was 23 weeks, and the main incorrect initial diagnoses were *M. pneumoniae* infection (17%) and sinusitis (7%) [42]. The most frequent symptoms were paroxysmal cough (22%) and post-tussive vomiting (13%), whereas whoop was reported by only 6% [42]. Indeed, as

reported in other countries, limited data from Israel and Iran show that pertussis in adults has a mild, sometimes atypical, clinical course and that the main manifestation is prolonged coughing [31, 42].

Whereas pertussis is a serious infection in infants and young children, and is generally much milder in adults, symptoms may be severe in adults, requiring hospitalisation, particularly in elderly adults with comorbid conditions [65, 66]. There were no studies identified for the review providing hospitalisation rates among older populations in the Middle East, but one retrospective study in Israel conducted between 1986 and 1991 reported that among 95 notified pertussis cases in a population aged 5–30 years, only two people (age unreported) required hospitalisation, and both had severe pneumonia as well as pertussis [42]. Similar to the Middle East, there are few hospital studies of pertussis in adults in other regions, yet the available data show that pertussis-related hospitalisation is uncommon among younger adults. For example, in a study in Australia in 2008–2011, 47% of pertussis-related hospitalisations were among infants aged < 1 year, and the lowest hospitalisation rates were among those aged 15–24 years [67]. In another hospital study in New Zealand in 2008–2009, two-thirds of pertussis-related hospitalised cases were infants aged < 1 years, and there were no hospitalisations in adults aged 45–64 years [68].

Global Burden of Disease (GBD) estimates of mortality in children aged < 5 years in 2015 varied across the Middle East, from 5.5/1000 in the UEA and 14.7/1000 in Iran to 53.6/1000 in Yemen, compared with the global rate of 41.4/1000 [69]. Based on an analysis of published literature, the GBD estimates of pertussis-related mortality in Iran in 2010 were 0.3025/100,000 in children aged < 5 years and 0.0009/100,000 in people aged 15–49 years [46]. However, among notified pertussis deaths in Iran in 2015, the mortality rate among young children was higher than previous GBD estimates at 0.176/1000 live births among children aged < 5 years [45]. The pertussis CFR was reported by one study, which showed that in Israel in 1999–2016, there were 19 deaths in infants, at a CFR of 0.7% [44]. The mortality rates reported in Iran and Israel are in line with those from other high- and middle-income countries, which show that although pertussis-related deaths are likely underestimated in all age groups, pertussis deaths are uncommon among young children and extremely uncommon in healthy adults [13, 19].

The main limitation of this review is that it provides a narrative analysis, with no statistical comparisons. However, the mix of surveillance methods for reporting pertussis incidence, different diagnostic tests used, varying levels of antibody cut-off values, and use of various international measures meant that it was not possible to calculate any meaningful average value in any group. Regarding antibody cut-off values, among studies providing information, the definition of laboratory-confirmed cases ranged from PT IgG levels > 20 EU/ml to PT IgG levels ≥ 100 EU/ml, and several studies stated that cases were seropositive for pertussis based on PCR or ELISA, yet did not state the cut-off value and/or which test was used.

The strengths of this study were that is used an established systematic review methodology and that it confirms, alongside pertussis notifications reported to WHO, that pertussis is circulating throughout the Middle East. However, most of the articles identified for the review were from Iran, Israel, and Turkey, meaning that the geographical scope was limited. This would suggest that more research is needed in Middle Eastern countries to confirm the extent and age profile of pertussis, although it should be noted that since the search was restricted to English language papers, some studies published in a non-English language might have been missed.

CONCLUSIONS

Surveillance data are weak or missing in some countries in the Middle East, yet surveillance studies, mainly from Iran, Israel, and Turkey, show that in common with other regions, pertussis is circulating in adolescents and adults. Greater recognition of the pertussis infection among older populations and improved national passive and active surveillance are

needed to better understand the transmission dynamics and burden of pertussis in the Middle East.

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