Infect Dis Ther (2021) 10:2071–2118
https://doi.org/10.1007/s40121-021-00520-9

REVIEW

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

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Received: June 25, 2021 / Accepted: July 30, 2021 / Published online: August 26, 2021


## ABSTRACT

Pertussis (whooping cough) epidemics persist globally despite high vaccine coverage among infants and young children. The resurgence of pertussis in high-income countries is partly due to waning vaccine immunity, resulting in a pool of unprotected adolescents and adults. However, pertussis is generally less severe in adolescents and adults, and this difference in presentation means it can often be unrecognised by healthcare professionals, meaning that it is largely 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 and mortality in school-aged children, adolescents and adults in Europe. A formal statistical comparison (e.g. using meta-analyses) was not possible because of the mix of methodologies reported. There were 69 epidemiological studies and 19 mortality studies identified for review. Over the past decade, the reported incidence of notified pertussis cases varied widely between European countries, which is likely associated with differences in surveillance systems, diagnostic techniques and reporting regulations. However, several studies show that pertussis is circulating among adolescents and adults in Europe, and although pertussis-related morbidity and mortality are highest in infants, there is evidence that adults aged > 50 years are at increased risk. For example, in a hospital-based surveillance study in Portugal, between 2000 and 2015, 94% of hospitalised pertussis cases were infants aged < 1 year, with a case fatality rate (CFR) of 0.8%; however, among hospitalised adult cases of pertussis, the CFRs were 11.5% (aged 18–64 years) and 17.4% (aged > 65 years). Very few European countries currently include pertussis boosters for adults in the national immunisation strategy. In addition to increasing pertussis vaccination coverage in adolescents and adults, mitigation strategies in European countries should include improved diagnosis and treatment in these populations.

**Keywords:** Pertussis; Whooping cough; Epidemiology; Burden; Children; Adolescents; Adults; Europe

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s40121-021-00520-9.

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**Key Summary Points**

A systematic search was undertaken to identify information on pertussis epidemiology and mortality in school-aged children, adolescents and adults in Europe.

There were 69 epidemiological studies and 19 mortality studies identified for review.

Over the past decade, the reported incidence of notified pertussis cases varied widely between European countries, However, several studies show that pertussis is circulating among adolescents and adults in Europe, and although pertussis-related morbidity and mortality are highest in infants, there is evidence that adults aged > 50 years are at increased risk.

Very few European countries currently include pertussis boosters for adults in the national immunisation strategy. In addition to increasing pertussis vaccination coverage in adolescents and adults, mitigation strategies in European countries should include improved diagnosis and treatment in these populations.

## INTRODUCTION

*Bordetella pertussis* is a highly contagious pathogen that is transmitted in aerosol droplets during coughing and sneezing. Historically, whooping cough, caused by *B. pertussis* infection, was a leading cause of death in young children and mass vaccination over the past 50 years has resulted in a large decline in global prevalence [1]. In most high-income countries, the national immunisation programme (NIP) includes a five-dose diphtheria-tetanus-acellular pertussis (DTaP) schedule for infants, toddlers and pre-school children, with coverage rates of > 95% [1]. Despite this, pertussis has re-emerged in several developed countries, representing a major public health concern [2]. Over the past 10 years, epidemic outbreaks of pertussis have been observed every 3–5 years, and between 2008 and 2015 there were sizeable spikes in pertussis cases in various countries, including the US, Canada, Australia, the UK, The Netherlands and Japan [3–7].

The resurgence of pertussis in countries with high vaccination coverage has been hypothesised to result from various factors, such as: the differential immunity and durability of responses elicited by acellular (aP) compared with whole-cell (wP) pertussis vaccines; linked-epitope suppression reducing the scope of epitopes involved in *B. pertussis* clearance to vaccine antigens; antigen imbalance with high predominance of PT; an epidemiologic shift resulting from waning of immunity in older children adolescents and adults; improved reporting systems and diagnostic methods; and a possible shift in circulation of the pathogen in pertactin-native strains [2, 8].

Although the highest burden of severe cases is among unvaccinated or partly vaccinated infants, epidemiological studies over the past 2 decades in various countries show that there has been a gradual shift in the age-specific peak of notified pertussis cases away from young children and towards adolescents and adults [9]. However, pertussis is often not suspected in older children and adults, leaving highly contagious individuals to spread infection via aerosol droplets for about 21 days after the onset of cough [10]. During pertussis outbreaks in several countries in 2012, whereas infants were the most affected age group, the proportion of affected adults was often much higher compared with recent years, indicating that adults play a major part in the transmission dynamic [11].

To evaluate the epidemiology, burden and mortality of pertussis infection in older children, adolescents and adults in European countries, we performed a systematic literature search and review of published studies of pertussis infection.

# METHODS

A systematic search of the literature was conducted using EMBASE, Medline and BIOSIS on 17 June 2019 to identify articles about the global epidemiology and mortality of pertussis. 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. 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 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 and mortality of pertussis by age. In the absence of standardised definitions, we categorised them by the following groups: young children (aged 4–9 years), adolescents (aged 10–18 years), adults (aged $\geq$ 19 years) and older adults (aged $\geq$ 60 years).

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

The systematic review was conducted to assess pertussis globally, and the results for Asia, the Middle East and Africa, are provided as parallel publications. The search results for the global analysis are shown in Supplement 3. This paper provides the results of articles identified with relevant data from countries in Europe.

### Serological Thresholds for Infection

Polymerase chain reaction (PCR), culture and serology using immunoglobulin G (IgG)-based enzyme-linked immunosorbent assays (ELISAs) are laboratory methods used to diagnose pertussis. An international consensus meeting in 2007 recommended that pertussis toxin (PT) should be used as the test antigen and that the results should be expressed in international units (IU/ml) using World Health Organisation (WHO) international standards [12, 13].

A four-fold increase in anti-PT IgG concentration between samples is accepted as evidence of recent infection, yet there is currently no global consensus on cutoff thresholds for single-sample serology. The thresholds for anti-PT IgG seropositivity are usually defined based on the manufacturer's instructions for the ELISA test as well as previous experience [14–16]. In individuals who have not been vaccinated within 1 year of the serum sample, anti-PT IgG $\geq$ 62.5 IU/ml to $\geq$ 80 IU/ml is often used as the cutoff threshold indicating pertussis infection within 12 months and cutoffs of $\geq$ 100 IU/ml and $\geq$ 125 IU/ml as evidence of recent infection and acute infection, respectively [13, 17, 18].

### 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.

**Table 1** Overview of epidemiology studies of pertussis in Northern Europe

| **Country, design, period**<br>**Age, *N*** | **Laboratory method of diagnosis** | **Key findings** |
|---|---|---|
| Denmark [19] | PCR or culture (from 2002) | 2013 results |
| Population-based, national surveillance | | Age years: no. cases (incidence/100,000) |
| 1995 to 2013 | | ≤ 90 days: 15 |
| All ages | | 0: 64 (110) |
| 13,269 confirmed cases | | 1–4: 63 (25) |
| | | 5–9: 37 (11) |
| | | 10–14: 72 (21) |
| | | 15–19: 39 (11) |
| | | 20–29: 25 (4) |
| | | 30–39: 52 (7) |
| | | 40–49: 71 (9) |
| | | ≥ 50: 63 (3) |
| | | Total: 486 (9) |
| Denmark [21] | PT IgG > 99.9 IU/ml | 2.6% |
| Healthcare based, case surv eillance | PT IgG > 44 IU/ml | 10.9% |
| October 2006 to June 2008 | *N* = 178 with cough 2 weeks–3 months: | 3.4% |
| > 8–87 years | PT IgG > 99.9 IU/ml | |
| 265 patients with cough of unknown aetiology | PT IgG > 44 IU/ml | 12.4% |
| Denmark [20] | PT IgG > 75 IU/ml | 3.0% |
| Population-based, active surveillance | | 3.3/100,000 in 2008 |
| 2006 to 2008 | | |
| 19–72 years | | |
| 3340 random sample | | |
| Finland [22] | Culture | 29 cases |
| Case surveillance (school outbreak) | | 40 symptomatic and 10 asymptomatic |
| 1992 to 1996 (five outbreaks) | | Year, *n*; no cases pertussis |
| School-aged children | | 1992, 39; 13 |
| 697 samples obtained | | 1993, 179; 4 |
| | | 1994, 156; 0 (11 parapertussis) |
| | | 1995, 123; 3 (10 parapertussis) |
| | | 1996, 200; 10 |

**Table 1** continued

| Country, design, periodAge, *N* | Laboratory method of diagnosis | Key findings |
|---|---|---|
| Finland [24] | Culture | 17 (77%) |
| Case surveillance (school outbreak) | Four-fold increase in anti-PT IgG agglutinin titres between paired samples | Of the 17 cases, the diagnosis was confirmed in 6 (35%) cases by culture and in 16 (94%) by serology |
| 1996 | Single value > 2 SD above mean value of unexposed immunised children | 8 (36%) had asymptomatic infection |
| 13 years | | |
| 22 children | | |
| Finland [23] | PCR and culture | 76 cases |
| Case surveillance (outbreak day-care center) | | Asymptomatic infection more common in pre-school children versus school children ($p < 0.001$) |
| 1992 | | Community of 12,691 people: incidence /100,000: |
| Children | | < 4 years: 317 |
| 12,691 in rural community | | 4–6 years: 1,838 |
| | | 7–15 years: 2535 |
| | | > 15 years: 248 |
| Finland [25] | PCR | 269 (22%) |
| Case surveillance (outbreak) | | Age years (n): |
| 1990–1993 | | < 1 (10): 20% |
| All ages | | 1–3 (43): 16% |
| 1233 routine samples | | 4–6 (56): 7% |
| | | 7–15 (455): 21% |
| | | 16–76 (107): 26% |
| | | Total (671): 27% |
| | | Asymptomatic cases more common < 7 years than other groups ($p < 0.001$) |
| Finland [26] | PCR and/or culture | 39/584 (6.7%) culture-positive |
| Healthcare based, case surveillance | | 95/564 (16.3%) PCR-positive |
| October 1994 to March 1997 | | |
| All ages | | |
| 584 patients with paroxysmal cough | | |

**Table 1** continued

| | | Age, years | Incidence/100,000 population | |
|---|---|---|---|---|
| | | | 1986 | 2007 |
| Sweden [29] | PCR and/or culture | 18 | 2.5 | 5.7 |
| Population-based, national s urveillance | | 19 | 4.9 | 3.4 |
| 1986 to 2007 | | 20–24 | 6.9 | 2.0 |
| All ages | | 25–29 | 14.3 | 2.4 |
| | | 30–34 | 14.9 | 1.3 |
| | | 35–39 | 7.1 | 2.7 |
| | | 40–44 | 3.2 | 4.4 |
| | | 45–49 | 1.5 | 3.1 |
| | | 50–54 | 3.3 | 1.9 |
| | | 55–59 | 2.7 | 2.1 |
| | | 60–64 | 2.1 | 2.4 |
| | | 65+ | 1.0 | 2.4 |
| Sweden [28] | Culture | Cases/100,000 person-years | | |
| Population-based, national surveillance | | 1998: 17 | | |
| October 1997 to December 2004 | | 1999: 25 | | |
| All ages | | 2000: 26 | | |
| 4700 pertussis isolates | | 2001: 11 | | |
| | | 2002: 13 | | |
| | | 2003: 7 | | |
| | | 2004: 16 | | |
| Sweden [30] | PCR and culture | Age: cases/100,000 person-years | | |
| Population-based, national surveillance | | 0–2 months: 225 | | |
| 1997 to September 2004 | | 3–4 months: 212 | | |
| Children | | 5–11 months: 31 | | |
| 123 confirmed cases | | 1 year: 8 | | |
| | | 2 years: 17 | | |
| | | 1–8 years: 19 | | |

**Table 1** continued

| | | Age, years | Incidence/100,000 population | |
|---|---|---|---|---|
| | | | 2016 | 2017 |
| Sweden [32] | PCR and culture | 18 | 11.1 | 8.3 |
| Population-based, national surveillance | | 19 | 6.5 | 5.7 |
| 2017 | | 20–24 | 5.7 | 6.2 |
| All ages | | 25–29 | 5.9 | 6.6 |
| 755 confirmed cases | | 30–34 | 6.5 | 7.5 |
| | | 35–39 | 7.4 | 9.8 |
| | | 40–44 | 5.4 | 8.5 |
| | | 45–49 | 3.7 | 5.5 |
| | | 50–54 | 2.9 | 4.3 |
| | | 55–59 | 2.5 | 2.3 |
| | | 60–64 | 2.8 | 3.6 |
| | | 65+ | 6.5 | 7.5 |
| Sweden [31] | PT IgG > 100 EU/ml | 1997 | | |
| Population-based, national surveillance | | 5–5.5 years: 21% | | |
| 1997 and 2007 | | 14.7–15.7 years: 7% | | |
| Children, adolescents, adults | | 2007 | | |
| 3420 children and adolescents at 1 year after the start of universal child vaccination (1997) | | 4–5 years: 4% | | |
| 2379 adolescents and adults ten years after vaccination (2007) | | 17–18 years: 16% | | |
| Norway [27] | PT IgG 20 to 30 IU/ml | 78% | | |
| Active-surveillance, military cohort | PT IgG > 80 IU/ml | 8.4% | | |
| 2004 | | | | |
| 19 to 27 years | | | | |
| 464 healthy Norwegian military recruits | | | | |

*PCR* polymerase chain reaction, *PT* pertussis toxin, *IgG* immunoglobulin, *SD* standard deviation

# EPIDEMIOLOGY

## Northern Europe

An overview of epidemiology studies in Northern European countries is shown in Table 1. Data were included from studies in Denmark [19–21], Finland [22–26], Norway [27] and Sweden [28–32].

### *Denmark*

In Denmark, the National Immunisation Programme (NIP) includes diphtheria-tetanus-acellular pertussis (DTaP) at 3, 5, 12 months and 5–7 years [33]. The pre-school booster was introduced in 2003, and a booster dose was introduced for adolescents aged 15–18 years circa 2013. There were three epidemiological studies identified for Denmark. In a study between 1995 and 2013, there were 13,269 PCR/culture-confirmed cases, and in 1995, 80% of all cases were children aged < 10 years, but in 2013, this figure had decreased to 34%. Similarly, in 1995, adults aged ≥ 20 years accounted for 14% of all cases but this figure increased to 43% in 2013. The median age of PCR/culture-confirmed cases gradually increased from 5.1 years in 1995 (interquartile range [IQR]: 1.5–8.7) to 15.7 years in 2013 (IQR: 4.8–41.5). Moreover, after the introduction of the pre-school booster, the age-specific peak shifted gradually towards older children [19]. In 1995–1997, the age-specific peak of infection was among children aged 3–5 years, yet in 2011–2013, the peak was among children aged 12–14 years [19]. In a population-based, active surveillance study of 3340 Danish adults in 2008, 3.0% had anti-PT IgG > IgG > 75 IU/ml, at an incidence of 3.3/100,000 [21]. In another study from 2006 to 2008, among 265 patients with cough of unknown aetiology, 2.6% had anti-PT IgG > 99.9 IU/ml, and among 178 patients with cough for > 3 months, 3.4% had anti-PT IgG > 99.9 IU/ml [20].

### *Finland*

In Finland, the NIP includes DTaP at 3, 5, 12 months and 4 years and an aP booster at 14–15 years [34]. All of the studies identified for Finland provided data from 1990 to 1997, i.e. before the introduction of a booster dose for school-aged children. The most recent analysis was a population-based, case-surveillance study conducted between 1994 and 1997, which showed that among 594 patients with paroxysmal cough (age ranged from 7 days to 74 years), 16.3% had PCR-confirmed pertussis [26]. In a school outbreak in Finland in 1996, among 22 children aged 13 years, 16 (94%) had positive serology (culture or paired sera), and (36%) had asymptomatic infection [24].

### *Sweden*

In Sweden, DTaP vaccines were introduced in 1996, administered at 3, 5 and 12 months. After the switch from wP to aP, the Public Health Agency of Sweden started to conduct enhanced surveillance to assess the effect of pertussis vaccinations on epidemiology and disease severity and to assess long-term protection with aP-containing combination vaccines [32]. The 20-year report from the Public Health Agency of Sweden includes surveillance data from 1996 to 2017 and shows that the incidence of pertussis decreased among groups targeted for vaccination and that during the epidemic years of 2014 and 2015 there was a threefold increase in the incidence of pertussis across all age groups and three infant deaths [32]. The incidence of pertussis across the general population was 7.1/100,000 person-years in 2014, 5.9/100,000 person-years in 2015, 6.5/100,000 person-years in 2016 and 7.5/100,000 person-years in 2017 [32]. Enhanced surveillance in Sweden showed that after the introduction of the aP primary vaccination schedule in 1996, the peak incidence of pertussis shifted from young children towards school-aged children in whom vaccine protection had waned, resulting in the introduction of a booster dose for children aged 4–5 years in 2007. Following this, the peak incidence of pertussis shifted to children aged 16–17 years, and in 2016, a Tdap booster dose was introduced to the NIP for adolescents. In 2017, based on 755 laboratory-confirmed cases among all ages, the largest increase in incidence compared with the previous year was among adults aged > 40 years (from 194 to 265 cases). Between 2016 and 2017, there was a decrease in

**Table 2** Overview of epidemiology studies of pertussis in Western Europe

| Country, design, period<br>Age, N | Laboratory method of diagnosis | Key findings |
|---|---|---|
| Austria [35] | PCR, culture, ELISA/seroconversion (paired sera) | 71 Incidence/100,000: |
| Hospital-based, case surveillance | | < 5 years: 2,385 |
| November 1995 to December 1998 | | 6–10 years: 1841 |
| < 16 years | | 11–16 years: 302 |
| 184 suspected cases | | |
| Belgium [36] | PCR, culture, | 208 in 2008 |
| Population-based, national surveillance | or fourfold rise in sera antibody titre | 356 in 2012 (71% increase) |
| 2008–2012 | | |
| All ages | | 181 cases were in children aged > 5 years |
| 342 notified cases | | |
| Belgium [38] | PT IgG > 50 IU/ml | *n* (%) |
| Population-based, active surveillance | | E. Flanders: 8 (6.7) |
| 2012 | | W. Flanders: 13 (10.2) |
| 20–29.9 years | | Liege: 4 (3.2) |
| 670 leftover serum samples | | Hainaut: 8 (13.1) |
| | | Brussel: 6 (4.8) |
| | | Bruxelles: 7 (6.0) |
| Belgium [37] | PT IgG > 100 IU/ml | *n* |
| Population-based, active surveillance | | E. Flanders: 16 |
| 2012 | | W. Flanders: 11 |
| 20–39 years | | Liege: 6 |
| 1500 left over serum samples | | Hainaut: 14 |
| | | UZ Brussels: 5 |
| | | CHU Bruxelles: 9 |
| France [41] | PCR | Incidence/100,000 |
| Healthcare based, case surveillance | | 103.6 (crude) |
| June 2013 to August 2014 | | 187.1 (extrapolated) |
| > 50 years | | |
| 129 suspected cases (cough 7–21 days) | | |

**Table 2** continued

| Country, design, periodAge, N | Laboratory method of diagnosis | Key findings |
|---|---|---|
| France [43]<br>Healthcare based, case surveillance<br>June 2013 to August 2014<br>> 50 years<br>129 suspected cases (cough 7–21 days) | PCR | Incidence/100,000<br>50 years: 187.1<br>Large cities: 131.1<br>Medium cities: 256.1<br>Rural: 187.1 |
| France [42]<br>Case surveillance (outbreak hospital)<br>July 1997<br>Adults<br>59 HCWs | PCR, culture,<br>or twofold rise in sera antibody titre | 10 (17%) |
| France [40]<br>Population-based, national surveillance<br>2000–2005<br>All ages<br>595 cases | PCR, culture, or serology | Aged 0–15 years: 20 cluster cases; 2 sporadic cases; 175 cases outside of healthcare<br>Aged > 15 years: 228 cluster cases; 2 sporadic cases; 101 cases outside of healthcare |
| France [44]<br>Healthcare based, case surveillance<br>March and December 1999<br>Mean 42 years<br>127 patients with cough < 7 days | PCR and/or a significant increase or decrease in anti-PT IgG between acute and convalescent sera | 70/183 confirmed cases; 32% (95% CI: 26–39)<br>PCR-positive: 36<br>Confirmed: 40 |

**Table 2** continued

| Country, design, periodAge, N | Laboratory method of diagnosis | Key findings | |
|---|---|---|---|
| France [46] | PT IgG 20–124 IU/ml | Age years | Cases (%) |
| Population-based, active sero-surveillance | | | |
| June to December 2005 | | 18–29 ($n$ = 134): | 43 (32.1) |
| 18–60 years | | | |
| 331 travellers attending vaccination clinic | | 30–39 ($n$ = 41): | 12 (29.3) |
| | | 40–49 ($n$ = 89): | 28 (31.5) |
| | | 50–60 ($n$ = 67): | 22 (32.8) |
| | PT IgG ≥ 125 IU/ml | 18–29 ($n$ = 134): | 18 (13.4) |
| | | 30–39 ($n$ = 41): | 1 (2.4) |
| | | | 5 (5.6) |
| | | 40–49 ($n$ = 89): | 1 (1.5) |
| | | 50–60 ($n$ = 67): | |
| France [45] | ≥ twofold change in anti–PT IgG or IgA change or PCR positive or culture positive | 103 (51.5%) | |
| Healthcare-based, case surveillance | | | |
| April to December 1999 | ≥ twofold change in anti–PT IgG or IgA | 40 (20) | |
| 18–88 years | ≥ twofold change in anti–PT IgA | 60 (30.5) | |
| 217 with persistent cough | PCR positive | 36 (18%) | |
| | Culture positive | 1 (0.5%) | |
| Germany [47] | PCR or anti-PT IgG levels > 95th centile of an age matched control cohort (defined as recent contact) | 180 | |
| Population-based, active surveillance | | 4.8/1000 person-years | |
| February 1993 to May 1995 | | | |
| Children | | | |
| 14,144 random sample | | | |

**Table 2** continued

| Country, design, periodAge, N | Laboratory method of diagnosis | Key findings |
|---|---|---|
| Germany [48]<br>Case surveillance (outbreak)<br>2005<br>Adults and children<br>75 cases in US military | PCR, culture, or clinical case with epidemiological link to a confirmed case | Age: cases (%)<br>< 2 months–4: 11 (15)<br>5–9: 19 (25)<br>10–14: 20 (27)<br>15–19: 7 (9)<br>≥ 20: 18 (24) |
| Germany [74]<br>Population based, case surveillance<br>1992–1994<br>Children and adults<br>122 households with index case | Culture or<br>Anti-PT, anti-FHA or anti-pertactin levels increase by 100% | 84 cases adults<br>179 cases children |
| Germany [49]<br>Population based, case surveillance<br>1984–1987<br>Adults<br>1260 cases with pertussis symptoms | Culture, anti-PT IgA titres ≥ 100 negative controls | 567 confirmed (45%)<br>Aged < 1 year, 324 cases (11%)<br>Aged > 20 years 169 (6%) |
| Germany [50]<br>Case surveillance (school outbreak)<br>October 2005 to March 2006<br>Children<br>104 cases | PCR, culture, or anti-IgG levels (cutoff not stated) | Years since last vaccination: cases (%)<br>< 5: 54 (1.9)<br>6: 48 (6.3)<br>7: 95 (14.7)<br>8: 79 (19.0)<br>9: 50 (32.0)<br>10: 17 (17.6)<br>> 10: 13 (23.1) |
| Germany [51]<br>Five former East German States<br>Population-based, national surveillance<br>1994–2007 | Notified cases | 2007<br>39.3/100,000 inhabitants |

**Table 2** continued

| Country, design, periodAge, N | Laboratory method of diagnosis | Key findings |
|---|---|---|
| Germany [52] | Notified cases | 80.4 cases/100,000 inhabitants |
| Brandenburg, case-cohort | | |
| Aged < 18 years | | |
| 2002–2012 | | |
| 3,219 cases | | |
| Ireland [53] | Culture, serology (test and cutoff not stated) | 7 confirmed (1 culture, 6 serology) |
| Case surveillance (outbreak) | | 4 probable |
| 2010 | | 56 possible cases |
| All ages | | Confirmed/ probable/possible cases/100,000: |
| 67 possible cases | | 0–4 years: 77.3 |
| | | 10–14 years 75.8 |
| | | > 19 years: 7.6 |
| Ireland [54] | PCR | *n* (%) |
| Hospital based, case surveillance | | Total 145 (10.95) |
| September 2003 to December 2009 | | 7 months–11 years: 27 (5.4) |
| All ages | | 12–15 years: 1 |
| 1324 suspected cases | | > 15 years: 0 |
| | Culture | Total 76 (5.7) |
| | | 7 months–11 years: 13 (2.6) |
| | | 12–15 years: 1 |
| | | > 15 years: 0 |
| Luxembourg [55] | Anti-PT IgG (no cutoff stated) | 40% |
| Active-surveillance, migrant cohort | | Aged 13–20 years 43.8% |
| May to September 2012 | | Aged 41–50 years 37.5% |
| 13–70 years | | |
| 172 migrants arriving from 30 countries of 67 cases in 2010 | | |

**Table 2** continued

| Country, design, periodAge, N | Laboratory method of diagnosis | Key findings |
|---|---|---|
| The Netherlands [58, 59]<br>Population-based, national surveillance<br>1996–2004 and 2005–2010<br>2001–2012<br>All ages<br>Notified cases | Notifications, various diagnostic methods | Overall: 32/100,000 (1996–2004) to 37/100,000 (2005–2010)<br>Aged ≥ 10 years: 15/100,000 (1996–2004) to 33/100,000 (2005–2010)<br>Overall: 63/100,000 (2001–2012)<br>Aged > 9 years: 6.8/100,000 (2005–2010) to 59.1/100,000 (2011–2012) |
| The Netherlands [56]<br>Case surveillance (outbreak convent)<br>1992<br>55–94 years<br>75 retired nuns and 24 staff members | PCR, culture, threefold rise in ≥ threefold rise in sera antibody titre or anti-PT IgG ≥ 100 IU/ml | Age: no. cases/total (%)<br>55–64 years: 8/16 (50)<br>65–74 years: 13/21 (62)<br>75–84 years: 16/27 (59)<br>85–94 years: 8/11 (73) |

**Table 2** continued

| Country, design, periodAge, N | Laboratory method of diagnosis | Key findings |
|---|---|---|
| The Netherlands [60]<br>Population-based, national surveillance<br>January 1998–2001 (without preschool booster) and 2002– December 2005 (with preschool booster)<br>All ages<br>Notified cases | Notifications, various diagnostic methods | Age: incidence/ 100,000 in 1998–2001: 2002–2005<br>0–5 months: 166.1: 132.3<br>6–11 months: 82.4: 84.9<br>1–4 years: 153.8: 86.5<br>5–9 years: 199.0: 168.6<br>10–19 years: 42.6: 68.2<br>20–59 years: 10.9: 15.7<br>≥ 60 years: 7.0: 11.7<br>Total: 34.3: 35.3 |
| The Netherlands [57]<br>Population-based, national surveillance<br>1994–1996<br>All ages<br>Notified cases | PCR, culture, ≥ fourfold rise in sera antibody titre or anti-PT IgG > 20 IU/ml (up to 1996), anti-PT IgG >100 IU/mL (from 1997) | Age: incidence/ 100,000:<br>0 years: 77.2<br>3–4 years: 87.4<br>5–9 years: 63.1<br>20–24 years: 1.2<br>30–44 years: 2.6–2.8 |
| The Netherlands [61]<br>Population-based, national surveillance<br>1989–1996<br>All ages<br>Notified cases | PCR, culture, ≥ fourfold rise in sera antibody titre or anti-PT IgG > 20 IU/ml (up to 1996), anti-PT IgG >100 IU/mL (from 1997) | Notified cases 1989: 1986<br>0 years: 21: 7<br>1–4 years: 1: 30<br>5–9 years: 42: 39<br>10–14 years: 10: 11<br>15–19 years: 1: 2<br>≥ 20 years: 5: 11<br>Total: 434: 2771 |

**Table 2** continued

| Country, design, periodAge, N | Laboratory method of diagnosis | Key findings |
|---|---|---|
| The Netherlands [63] | PT IgG ≥ 62.5 IU/mL | Age, no. cases (%) |
| Population-based, active surveillance | | 10–19 years: 81 (11) |
| February 2006 and July 2007 | | 20–34 years: 128 (9) |
| 10–79 years | | 35–49 years: 109 (9) |
| 7903 random samples | | 50–64 years: 118 (9) |
| | | 65–79 years: 144 (12) |
| The Netherlands [62] | PT IgG ≥ 50 IU/ml | 2012 (epidemic): 97/1000 person-years |
| Population-based, active surveillance | | |
| 2011–2014 | | 2013—2014 (low-epidemic): 16/1000 person-years |
| 10–18 years | | |
| 239 random samples | | |
| UK, England [70] | PCR | No. cases (%) reported cases |
| Population-based, national surveillance | PT IgG ≥ 70 IU/ml | < 1 month: 101 (1) |
| 2010 to 2015 | | 1–3 months: 386 (4) |
| All ages | | 4–11 months: 146 (2) |
| 9163 reported cases | | 1–9 years: 894 (10) |
| | | ≥ 10 years: 7616 (83 |
| UK, England [68] | PCR, culture | Incidence/100,000 |
| Population-based, national surveillance | | 2012: 17.6 |
| January 2013 to December 2015 | | 2013: 8.6 |
| All ages | | 2014: 6.2 |
| Notified cases | | 2015: 7.7 |

**Table 2** continued

| Country, design, periodAge, N | Laboratory method of diagnosis | Key findings |
|---|---|---|
| UK, England and Wales [67] | PT IgG $\geq$ 100 IU/ml | Incidence/100,000: |
| Population-based, national surveillance | | 1987: 211 |
| 1987 to 1998 | | 1988: 71 |
| < 10 years | | 1989: 160 |
| Notified cases | | 1990: 204 |
| | | 1991: 69 |
| | | 1992: 29 |
| | | 1993: 51 |
| | | 1994: 48 |
| | | 1995: 23 |
| | | 1996: 29 |
| | | 1997: 36 |
| | | 1998: 20 |
| UK, England and Wales [66] | PCR, culture | Age: no. cases 2002: 2012: |
| Population-based, national surveillance | | |
| 1982 to 2012 | | < 1 year: 98: 175 |
| All ages | | 1–9 years: 59: 121 |
| Notified cases | | 3–6 years: 60: 104 |
| | | 6–10 years: 48: 67 |
| | | 10–15 years: 71: 104 |
| | | 15–20 years: 80: 129 |
| | | 20–40 years: 346: 534 |
| | | > 40 years: 471: 793 |
| | | Total: 1233: 2027 |

**Table 2** continued

| Country, design, periodAge, N | Laboratory method of diagnosis | Key findings |
|---|---|---|
| UK, England [65] | PCR, culture | Total cases (year) |
| Population-based, national surveillance | | 304 (2010); 629 (2011); 5909 (2012); 3795 (2013) |
| 2012 to 2013 | | |
| All ages | | Age; year, cases (%) |
| Notified cases | | 1–4 years: 2010, 7 (2.3); 2011, 10 (1.6); 2012, 58 (1.0); 2013, 41 (1.1) |
| | | 5–19 years: 2010, 59 (19.4); 2011, 124 (19.7); 2012, 1128 (19.1); 2013, 669 (17.1) |
| | | ≥ 20 years: 2010, 186 (61.2); 2011, 349 (55.5); 2012, 4311 (73.0); 2013, 2984 (78.6) |
| UK [71] | PCR | 62 (36.5%) |
| Healthcare-based, case surveillance | | |
| October 2001 and March 2005 | | |
| 6.5–12.5 years | | |
| 62 with cough ≥ 2 weeks | | |
| UK [72] | PT IgG ≥ 100 IU/ml | 20/56 (35.7%) |
| Healthcare-based, case surveillance | | |
| 1995 | | |
| 16–60 years | | |
| 56 patients with cough | | |

**Table 2** continued

| Country, design, periodAge, N | Laboratory method of diagnosis | Key findings |
|---|---|---|
| UK [73]<br>Healthcare-based, case surveillance<br>March 1996 to November 1997<br>5–78 years (mean 31 years)<br>145 with cough ≥ 3 weeks | PT IgG and IgA: ≥ 2 antibodies with levels ≥ 2 SD or at least one antibody with a level ≥ 3 SD, above the mean of the age matched controls | 40 (28%) |

*CI* confidence interval, *PCR* polymerase chain reaction, *PT* pertussis toxin, *IgG* immunoglobulin, *HCW* healthcare worker, *SD* standard deviation

cases among children aged 15–19 years (from 58 to 52 cases) and an increase among children aged 10–14 years (from 69 to 104 cases) [32].

Published studies identified for review provided epidemiological data in Sweden up to 2007 and these studies were used to inform the Public Health Agency of Sweden on vaccination policy [28–31]. In a study in Sweden that tracked the incidence of culture- or laboratory-confirmed cases over a 10-year period (1997–2007), the incidence of pertussis was reduced among adults after the introduction of infant DTaP vaccination, particularly among those aged 25–35 years [29]. There were two further serosurveys studies in Sweden, one in 1997 when the new pertussis vaccination programme had been in place for 1 year ($n$ = 3420) and the other was performed in 2007 to assess the effect of vaccination on anti-PT IgG antibody prevalence ($n$ = 2379). In younger children, the proportion with anti-PT IgG ≥ 50 and ≥ 100 European units (EU)/ml was significantly higher in 1997 than in 2007 for both cutoffs. For all adults aged ≥ 20 years, the difference in proportions with anti-PT IgG ≥ 50 EU/ml was close to statistical significance comparing 1997 with 2007, yet this was not the case at anti-PT IgG ≥ 100 EU/ml. In the 1997 samples of children, there was a significant downward trend in the rates of those above both cutoffs, and the rates of anti-PT IgG ≥ 50 EU/ml for three sampled age groups aged between 5 and 15 years ranged from 21% at age 5.0–5.5 years to 7% at age 14.7–15.7 years. In 2007, among samples of children, there was a significant continuous upward trend at both cutoff points, and the rates of anti-PT IgG ≥ 50 EU/ml for four sampled age groups between 4 and 18 years ranged from 4% at age 4–5 years to 16% at 17–18 years [31].

### *Norway*

In Norway, the NIP includes DTaP at 3, 5, 12 months and 7 years, and an aP booster at 18 years [34]. One study in Norway showed that among 464 healthy military recruits in 2004, the rate of anti-PT IgG > 80 IU/ml was 8.4% [27].

## Western Europe

An overview of epidemiology studies in Western European countries is shown in Table 2. Countries for which study data were available included Austria [35], Belgium [36–38], France [39–46], Germany [47–52], Ireland [53, 54], Luxembourg [55], The Netherlands [56–63], Switzerland [64] and the UK [65–73].

### *Austria*

In Austria, the NIP includes three doses of aP from aged 3–12 months, minimum 6-month interval after second dose, a booster dose in children aged 8–9 years, and every 10 years in adults and every 5 years in adults aged ≥ 65 years [34].

**Table 3** Overview of epidemiology studies of pertussis in Central and Eastern Europe Western Europe

| Country | Design, period | Age, *n*, sample type |
|---|---|---|
| Bulgaria [77]<br>Hospital-based, active-surveillance<br>2009 to 2016<br>Children and adolescents<br>28 cases | PCR | < 1 year: 18 cases<br>1–3 years: 6 cases<br>10–14 years: 2 cases |
| Bulgaria [78]<br>Population-based, national surveillance<br>2009 to 2015<br>All ages<br>Notified cases | PCR | < 1 year: 12<br>1–4 years: 9<br>5–9 years: 7<br>10–19 years: 0<br>≥ 20 years: 1 |
| Bulgaria [79]<br>Population-based, active surveillance<br>2001–2008<br>> 7 years<br>5887 samples | Pertussis antibody levels > 0.1 IU 'fully protected' | Age years (n)<br>7–15 (609): 30.7%<br>16–25 (1977): 16.55%<br>26–35 (1766): 38.75%<br>36–45 (758): 21.65%<br>46–55 (581): 16.65%<br>> 56 (506): 0.6% |
| Estonia [96]<br>Hospital based, case surveillance<br>April 2012 to December 2014<br>All ages<br>549 with cough ≥ 7 days | PCR positive and single PT-IgG was > 100 IU/ml<br>or<br>PT-IgG 40–100 IU/ml and PT-IgA > 12 IU/ml | Total: 22 cases<br>Age, % cases<br>< 1 year: 5.6%<br>1–9 years: 5.6%<br>10–17 years: 6.3%<br>18–64 years: 3.1%<br>≥ 65 years: 0% |

**Table 3** continued

| Country | Design, period | Age, *n*, sample type |
|---|---|---|
| Estonia [165] | Culture or PT IgA/IgM > 12 IU/ml | 54 cases (36%) |
| Case surveillance (school outbreak) | | Age: no. cases |
| 2003 | | 7 years: 1 |
| 10–16 years | | 8 years: 5 |
| 150 students | | 9 years: 5 |
| | | 10 years: 7 |
| | | 11 years: 8 |
| | | 12 years: 8 |
| | | 13 years: 8 |
| | | 14 years: 3 |
| | | 15 years: 5 |
| | | 16 years: 4 |
| Estonia [82] | PT IgG ≥ 125 IU/ml | 2.0% |
| Population-based, active surveillance | PT IgG ≥ 62.5 to < 125 IU/ml | 5.6% |
| April to August 2012 | | |
| ≥ 7 years | | |
| 1053 random samples | | |
| Estonia [83] | PT IgG ≥ 62.5 to < 125 IU/ml | 2.7% |
| Population-based, active surveillance | PT IgG ≥ 125 IU/ml | 0.6% |
| January to February 2013 | | |
| 20–99 years | | |
| 3327 random samples | | |
| Czech Republic [81] | Serology assay | Age: incidence/100,000 |
| Population-based, active surveillance | | 0 year: 15.6 (2000); 4.4 (2001) |
| | | 1–4 years: 9.1 (2000); 5.6 (2001) |
| 2000–2001 | | 5–9 years: 6.6 (2000) and 4.7 (2001) |
| 0–64 years | | 10–14 years: 11.3 (2000); 8.2 (2001) |
| 3194 random samples | | ≥ 20 years: 0.1 (2000); 1.2 (2001) |

**Table 3** continued

| Country | Design, period | Age, *n*, sample type |
|---|---|---|
| Czech Republic [80] | PCR | Age: incidence/100,000 in 2008 |
| Population-based, national surveillance | | 0 year: 26.7 |
| 1988 to 2008 | | 1–4 years: 6.4 |
| 0–24 years | | 5–9 years: 22.6 |
| Notified cases | | 10–14 years: 79.8 |
| | | 15–19 years: 21.8 |
| | | 20–24 years: 0.8 |
| Czech Republic [98] | PT IgG $\geq$ 10 units/ml | 39.9% (799/2000, 95% CI 37.8, 42.1%) |
| Population-based, active surveillance | | By age group, highest seropositive rates in 18–29 years: 1.46% ($p$ = 0.002) |
| October 2011 until May 2012 | | |
| $\geq$ 18 years | PT IgG $\geq$ 62.5 units/ml | 2 (0.40%), 8/2000: 95% CI 0.17, 0.79%) |
| 2000 samples; not vaccinated within 5 years | PT IgG $\geq$ 125 units/ml | 0 |
| Hungary [84] | PT IgG > 18 EU/ml | 14.8% |
| Population-based, active surveillance | PT IgG > 70 EU/ml | 1.1% |
| April 2014 to April 2015 | PT IgG > 110 EU/ml | 0.1% |
| $\geq$ 18 years | | |
| 1999 people without vaccination within 12 months | | |
| Poland [86] | Culture and serology | Age: incidence/100,000 |
| Population-based, national surveillance | | All: 330 (1996); 2411 (2001) |
| 1999–2001 | | 0–1 year: 14.5 (1996); 21.7 (2001) |
| 0–13 years | | Age 2–5 years: 3.2 (1996); 21.7 (2001) |
| Notified cases | | 6–9 years: 2.9 (1996); 32.6 (2001) |
| | | 10–13 years: 2.0 (1996); 34.0 (2001) |

**Table 3** continued

| Country | Design, period | Age, *n*, sample type |
|---|---|---|
| Poland [91]<br>Population-based, national surveillance<br>1990 to 2000<br>All ages<br>Notified cases | Bacteriology, immunofluorescence, or serology | Proportion of cases:<br>Aged < 1 year: 37.0% (1976–1989); 24.0% (1990–1996); 7.7% (1997–2000)<br>Aged 0–4 years: 73.9% (1976–1989); 65.9% (1990–1996); 24% (1990–1996)<br>Between 1985 and 1997<br>Aged 5–9: twofold increase cases<br>Aged 10–14 years: sevenfold increase in cases |
| Poland [89]<br>Population based, case surveillance<br>2005 to 2009<br>All ages<br>1455 cases | Confirmed: PCR or significant increase in IgG or IgA antibodies<br>Probable: case definition, not laboratory confirmed, but epidemiologically linked to confirmed-suspected: only clinical symptoms | Incidence/100,000:<br>< 1 year: 13.3 (2006); 32.7 (2007)<br>10–14 years: 11.8 (2006); 68.5 (2008<br>10–19 years: 60% of cases<br>20–64 years: 20% of cases |
| Poland [92]<br>Population-based, national surveillance<br>2011<br>All ages<br>1699 notified cases | ELISA and immunoassays, *n* = 1568<br>Culture, *n* = 1<br>Clinical diagnosis, *n* = 100 | Age: incidence/100,000 (%)<br>All: 4.3<br>3 years: 20.8<br>≤ 15 years: 2.5<br>10–14 years: 20.3<br>> 15 years: 2.5 |
| Poland [93]<br>Population-based, national surveillance<br>2012<br>All ages<br>4684 notified cases | ELISA and immunoassays, *n* = 4244<br>Culture, *n* = 1<br>Clinical diagnosis, *n* = 439 | Age: incidence/100,000<br>All: 12.2<br>3 years: 39.9<br>10–14 years: 56.5<br>> 15 years: 7.8 |

**Table 3** continued

| Country | Design, period | Age, *n*, sample type |
|---|---|---|
| Poland [94]<br>Population-based, national surveillance<br>2013<br>All ages<br>2182 notified cases | ELISA and immunoassays, *n* = 2035<br>Culture, *n* = 0<br>Clinical diagnosis, *n* = 147 | Age: incidence/100,000<br>All: 5.7<br>3 years: 34.9<br>10–14 years: 16.4<br>> 15 years: 3.5 |
| Poland [95]<br>Population-based, national surveillance<br>2014<br>All ages<br>2100 notified cases | ELISA and immunoassays, *n* = 1950<br>Culture, *n* = 0<br>Clinical diagnosis, *n* = 148 | Age: incidence/100,000<br>All: 5.5<br>3 years: 33.0<br>10–14 years: 22.1<br>> 15 years: 2.9 |
| Poland [166]<br>Population-based, national surveillance<br>2015<br>All ages<br>4956 notified cases | Notified cases | Incidence 12.89/100,000 |
| Poland [90]<br>Healthcare based, case surveillance<br>July 2009 to April 2011<br>All ages<br>1232 patients with persistent cough | PT IgA and/or IgG levels > 3 standard deviations versus age-stratified controls | 288 confirmed cases<br>Adjusted annual incidence: 201.1/100,000 person-years |
| Slovenia [97]<br>Population-based, national surveillance<br>1990 to 2006<br>All ages | Notified cases | Incidence/100,000 in 2006<br>All: 27.5<br>10–14 years: 220<br>5–9 years: 167<br>Infants: 144<br>9 years: 365.5 |

**Table 3** continued

| Country | Design, period | Age, *n*, sample type |
|---|---|---|
| Slovenia [87] | PT IgG 5.0–9.9 U/ml | n; % (95% CI) |
| Population-based, active surveillance | | 510; 14.9% (11.81–17.99) |
| | PT IgG 10.0–50.9 U/ml | 2207; 64.6% (62.61–66.59%) |
| 2000 | PT IgG 51.0–124.9 U/ml | 228; 6.7%, (3.5–9.9%) |
| 0–60 years | PT IgG > 125 U/ml | 80; 2.3% (0.9–5.5%) |
| 3418 random samples | | |

*CI* confidence interval, *PT* pertussis toxin, *IgG* immunoglobulin

One study identified from Austria assessed serology among 184 suspected cases in children aged up to 16 years between 1995 and 1998. The results showed that the majority of cases were among un- or partly vaccinated infants, and the incidence of cases, confirmed by PCR and culture, of PT IgG or IgA seroconversion among paired sera was 71 cases/100,000 population overall. The incidence of pertussis among children with cough was estimated at 1841 cases/100,000 for those aged 6–10 years and at 302 cases/100,000 population among children aged 11–16 years [35].

### *Belgium*

In Belgium, the NIP includes DTaP at 2, 3, 4, 15 months and 5 years and aP booster at 14–16 years (added to the schedule in 2009), then every 10 years, and for pregnant women at 24 to 32 weeks gestation [34]. In a population-based surveillance study in Flanders, Belgium, among notified cases of all ages (PCR, culture or serology), there were 208 cases in 2008 and 356 cases in 2012, representing a 71% increase, of which 181 cases were in those aged > 5 years [36]

### *France*

In France, the NIP was modified in 2013, from a recommended DTaP vaccination at 2, 3, 4 and 16–18 months to 2, 4 and 11 months. The infant series has been mandated since 2018. The programme has also recommended aP vaccination at 6 years since 2013 and at 11–13 years since 1998 [34]. In 2006, a Tdap booster was introduced for individuals aged 25 years who had not received pertussis vaccine within the previous 5 years and for those aged 25–39 years who had not received Tdap booster. A booster dose every 20 years is currently recommend for adults in France as well as cocooning of unvaccinated infants [34].

In a healthcare-based surveillance study of adults presenting with persistent cough during a 7-month period in 1999, of 2017 patients, 200 had laboratory-confirmed pertussis including 1 culture-positive case, 36 PCR-positive, 40 with ≥ twofold change in anti-PT IgG and 60 with ≥ twofold change in anti-PT IgA [45]. The estimated annual incidence of pertussis in adults was 884 cases/100,000 population (95% CI, 601–1199 cases/100,000 population) [45]. In a serosurvey of adults attending a French travel vaccination clinic between June and December 2005, 7.6% overall and 13.4% of those aged 18–29 years had anti-PT IgG ≥ 125 IU/ml [46].

A study of outbreaks in France between 2002 and 2005 showed that of 595 notified pertussis cases, of which < 50% were confirmed by PCR, culture or serology, there were 197 and 331 cases in individuals aged < 15 years and > 15 years, respectively [40]. The most recent studies in France were population-based, case-surveillance analyses, reporting a crude incidence of PCR-confirmed pertussis of 145/100,000 in 2008–2009 in adolescents and adults and of 103–256/100,000 in 2013–2014 in adults aged > 50 years [39, 41, 43].

**Table 4** Overview of epidemiology studies of pertussis in Southern Europe

| Country | Design, period | Age, *n*, sample type |
|---|---|---|
| Cyprus [99] | Laboratory confirmed, PT IgA (no cutoff stated) | 24 cases |
| Case surveillance (outbreak) | | 2 cases aged < 10 years |
| June to July 2003 | | 16 cases aged 10–20 years |
| All ages | | 6 cases aged > 20 years |
| 71 suspected cases | | |
| Greece [100] | PCR | 245 cases |
| Hospital-based, case surveillance | | 85% of those aged ≥ 8 years |
| 1999–2008 | | 45% of those aged < 4 years |
| All ages | | 45 (78.9%) household contacts |
| 283 children hospitalised/ clinical diagnosis | | 23 (69.7%) adults with chronic cough |
| 57 household contacts of children with laboratory diagnosis | | Among children with a clinical diagnosis, 35 had a close contact with pertussis |
| 33 adults with chronic cough | | |
| Greece [101] | Positive anti-PT and anti-FHA IgG | Age: no. cases/N (%): |
| Population-based, active surveillance | | 1–60 days: 13/32 (40.6) |
| January to October 2000 | | 2–12 months: 19/32 (59.4) |
| 1–80 years: 439 random samples | | 1–4 years: 21/34 (61.8) |
| | | 5–10 years: 36/58 (35.3) |
| | | 11–20 years: 40/72 (62.1) |
| | | 21–30 years: 42/74 (55.6) |
| | | 31–40 years: 24/36 (56.8) |
| | | 41–50 years: 49/59 (66.7) |
| | | > 50 years: 49/59 (83.1) |
| | | Total: 256/431 (59.4) |
| Italy [110] | PCR | 30 (15.8%) |
| Case surveillance (school outbreak) | | |
| April 2009 | | |
| Children: 71 suspected cases | | |

**Table 4** continued

| Country | Design, period | Age, *n*, sample type |
|---|---|---|
| Italy [109] | PCR | 78 positive samples: n (%) |
| Hospital-based, case surveillance | | 11 (1.7%) for B pertussis |
| September 2013 to December 2014 | | 2 (0.3%) for B parapertussis |
| 643 children admitted with lower respiratory tract infections | | 52 (8.1%) M pneumoniae |
| | | 9 (1.4%) C pneumoniae |
| | | 5 (0.8%) L pneumophila |
| Italy [107] | Notified cases | Age: incidence/100,000 (1998–2004) |
| Population-based, national surveillance | | |
| 1961 to 2013 | | 1–4 years: 10.5–81.8 |
| All ages | | 5–9 years: 12.1–116.4 |
| Notified cases | | Age: incidence/100,000 (2003–2004) |
| | | 1–4 years: 1.6–11.2 |
| | | 10–14 years: 2.5–13.6 |
| | | ≥ 15 years: 0.0–1.1 |
| Italy [102] | PT IgG > 3 times higher than negative sera | Age: incidence/100,000 (%) |
| Population-based, active surveillance | | 1– < 2: 273.90 (19.6) |
| March 1988 to November 1989 | | 2– < 3: 127.93 (36) |
| 6–19 years | | 3– < 4: 214.94 (42.6) |
| 3875 random samples (unvaccinated) | | 4– < 5: 200.39 (55.3) |
| | | 5– < 6: 151.15 (68.9) |
| | | 6–9: 59.16 (76) |
| | | 10–13: 12.83 (83) |
| | | 14– < 15: 4.46 (86) |
| | | 15–17: 1.75 (90) |
| | | 18–19: 1.53 (95) |
| Italy [103] | Culture or antibody titres > 2 SD higher than GMT of control group | Range/GM; n |
| Case series | | PT IgA: 214–374/271; 203 |
| 1998 to 1999 | | PT IgG: 122–913/305; 449 |
| Adults: 180 with chronic unexplained cough | | |

**Table 4** continued

| Country | Design, period | Age, *n*, sample type |
|---|---|---|
| Italy [104] | PT and FHA IgG 2 EU/ml, PRN IgG 3 EU/ml and PT IgA 10 EU/ml | Antigen: no. cases with titre > minimum level detection/N (%) |
| Active-surveillance, military cohort | | |
| 1994 to 1995 | | IgG PT: 298/416 (71.6) |
| 17–25 years | | IgG FHA: 412/416 (99.0) |
| 416 military recruits | | IgG PRN: 337/416 (81.0) |
| | | IgA PT: 66/416 (15.9) |
| Italy [105] | PT IgG ≥ 100 IU/ml | 40% of parents |
| Hospital-based, case surveillance | | |
| 2017 (publication date) | | |
| 168 parents of: 55 infants hospitalised for pertussis; 33 infants with respiratory infection; 57 healthy infants | | |
| Italy [108] | Clinical diagnosis | Aged 10–14 years, incidence: 366/100,000 |
| Healthcare-based, case surveillance | | |
| 2002 | | |
| Children aged < 15 years | | |
| Italy [106] | PT IgG 20–49 IU/ml | Age; no. cases/N (%) |
| Population-based, active surveillance | | 20–29 years; 54/239 (22.6) |
| April 2012 to March 2013 | | 30–39 years; 61/248 (24.6) |
| Adults: 639 random samples | | ≥ 60 years; 59/152 (38.8) |
| | | Total: 175/639 (27.2) |
| | PT IgG 50–99 IU/ml | Age; no. cases/N (%) |
| | | 20–29 years; 23/239 (9.6) |
| | | 30–39 years; 23/248 (9.3) |
| | | ≥ 60 years; 12/152 (7.9) |
| | | Total: 58/639 (9.1) |
| | PT IgG ≥ 100 IU/ml | Age; no. cases/N (%) |
| | | 20–29 years; 17/239 (7.1) |
| | | 30–39 years; 8/248 (3.2) |
| | | ≥ 60 years; 7/152 (4.6) |
| | | Total: 32/639 (5.0) |

**Table 4** continued

| Country | Design, period | Age, *n*, sample type |
|---|---|---|
| Spain [115]<br>Population-based, national surveillance<br>1982–2005<br>All ages<br>39,580 notified case | Laboratory-confirmed or epidemiological linked to a confirmed case | Incidence: 8.4/100,000 |
| Spain/Catalonia [121]<br>Population-based, active surveillance<br>1996<br>887 school children<br>1249 adults | PT IgG > 100 EU/ml | Age, no. cases; incidence/100,000<br>15–24 years: 36; 5.7<br>25–34 years: 8; 0.8<br>35–44 years: 5; 0.5<br>45–54 years: 5; 0.6<br>55–64 years: 1; 0.1<br>> 64 years: 1; 0.1<br>Total: 177; 0.1<br>Urban ≥ 10,000: 143; 0.98<br>Rural < 10,000:36; 0.97 |
| Spain [112]<br>Case surveillance (school outbreak)<br>May 2015<br>12–17 years<br>395 students<br>and 47 teachers | PCR or serology or epidemiologically-linked | Birth cohort (age): attack rate %<br>2002 (17 years): 37<br>2001 (16 years): 12<br>2000 (15 years): 8<br>1999 (14 years): 4<br>1998 (13 years): 3<br>1999 (14 years): 2 |
| Spain [124]<br>Active surveillance HCW cohort<br>2004 (publication date)<br>≥ 25 years<br>487 hospital personnel | PT IgG > 11.0 VE | Total: 51.7%<br>Age (N); % (95% CI)<br>19–24 years (96); 51.0 (37–65)<br>25–34 years (190); 46.3 (36–57)<br>35–44 years (100); 53.0 (40–66)<br>≥ 45 years (101); 56.4 (44–69) |

**Table 4** continued

| Country | Design, period | Age, *n*, sample type |
|---|---|---|
| Spain [123] | PT IgG (cutoff not stated) | % (95% CI) |
| Population-based, active surveillance | | Male (n = 204); 72.5 (66.4–78.7) |
| 1996 | | Female (n = 949); 69.7 (66.7–72.6) |
| 19–39 years | | |
| 1153 samples from health personnel | | |
| Spain [125] | PT IgG > 36–44 IU/ml | 22 (10.0%) |
| Active surveillance, HCW cohort | PT IgG > 45–99 IU/ml | 23 (10.5%) |
| June 2008 and December 2010 | PT IgG > 100 IU/ml | 10 (4.5%) |
| Adults: 220 HCWs | | |
| Spain [126] | PT IgG ≥ 0.3 OD | 228 (31.8%) |
| Hospital-based, HCW cohort | PT IgG ≥ 1.0 OD (≥ 100 EU/ml) | 24 (3.3%) |
| 22 November 2012 to May 2013 | | |
| 731 adults | PT IgG ≥ 1.5 OD | 5 (0.7%) |
| Spain [127] | PT IgG ≥ 2.0 OD | 5 cases 46.0/100,000 |
| Population-based, case surveillance | | 2–5 years: 2 cases 76/100,000 |
| February 2001 to January 2002 | | 6–10 years: 2 cases; 59/100,000 |
| ≤ 15 years | | 11–15 years: 1 case; 28/100,000 |
| 61 children with cough ≥ 2 weeks | | |
| Spain [114] | Notified cases | Incidence rate ratio (95% CI) for 2010–2012 versus 1998–2001 |
| Population-based, national surveillance | | Total: 4.34 (4.13–4.55) |
| 2010 to 2012 | | 30–39 years: 13.16 (9.63–17.98) |
| All ages | | 40–49 years: 21.47 (13.64–33.81) |
| | | 15–49 years: 14.06 (11.63–16.99) |
| | | ≥ 50 years: 16.91 (11.40–25.09) |
| Spain [122] | Suspected/clinical diagnosis, confirmed/laboratory diagnosis (test not stated) | Incidence/100,000 |
| Population-based, national surveillance | | Aged 5–9 years: 3.04 |
| 1997 to 2010 | | Aged 10–14 years: 3.59 |
| All ages | | Aged 15–44 years: 0.29 |
| 3397 suspected/confirmed cases | | Aged > 45 years: 0.1 |

*PCR* polymerase chain reaction, *PT* pertussis toxin, *IgG* immunoglobulin, *SD* standard deviation

### *Ireland*

In Ireland, the NIP includes DTaP at 2, 4, 6 months and 4–5 years and a Tdap booster at 12–13 years. Pertussis vaccination for pregnant women between 27 and 36 weeks' gestation was introduced in 2013 [34].

There were two studies from Ireland including a case-surveillance study of a school outbreak in 2010 and a hospital-based assessment of suspected cases from 2003 to 2009. In the school outbreak study, among possible cases including 67 children and adults, one case was confirmed by culture and six by serology [53]. The attack rate of confirmed/probable/possible cases was 77.3/1000 population in children aged 0–4 years and 75.8/1000 population in children aged 10–14 years. Four cases were hospitalised, including three neonates and one adult aged 60 years. There were 20 cases in those aged > 19 years, at an attack rate of 7.6/1000 population. In the hospital study of 1324 suspected cases, 76 (5.7%) were culture positive and 145 (10.95%) were PCR positive; for both culture and PCR, the majority of cases were aged < 6 months [54]. In the group aged 7 months–11 years, the rates by PCR and culture were 5.4% and 2.6%, respectively. In the group aged 12–15 years, there was one positive case each by PCR and culture, and there were no cases in the group aged > 15 years [54].

### *Germany*

In Germany, the NIP includes DTaP at 2, 3, 4 and 11–14 months and an aP booster dose at 5–7 years and for children aged 9–17 years. An aP booster is recommended for adults 10 years after the last aP dose [34]. Before the introduction of the current infant pertussis schedule in reunified Germany in 1991, the incidence of pertussis was lower in former East Germany than in former West Germany, which was associated with the different NIPs used during the 1970s and 1980s between the different states [51]. In reunified Germany in 1995, infant aP vaccine replaced infant wP vaccine, and an adolescent booster dose was introduced in 2000 [51].

In an analysis of pertussis epidemiology in five former East German States, in 2007, the incidence of pertussis was 39.3 cases/100,000 inhabitants, with an increase in the proportion of adult cases from 20% in 1995 to 68% in 2007. From 2002, the age-specific peak incidence was in children aged 5–9 years and 10–14 years, reaching an incidence of > 300 cases/100,000 inhabitants in two of the states [51]. In a further analysis of a cohort in Brandenburg comprising 3219 cases among children aged < 18 years between 2002 and 2012, the incidence of pertussis was 80.4 cases/100,000 inhabitants. The peak incidences shifted from children aged 5–14 years in 2004–2006 to children aged 10–17 years in 2011–2012, and in 2012, the peak incidence was among adolescents aged 15–17 years [52]. The aim of the cohort study was to assess vaccine effectiveness (VE) over time following the change from infant wP vaccine to infant aP vaccine and the introduction of the adolescent booster dose. The study showed that aP vaccine was effective; however, the high incidence of pertussis among school children and adolescents was likely associated with waning vaccine immunity and low vaccine coverage of booster doses [52].

There were five further epidemiological studies in Germany, of which two reported pertussis epidemiology this century. The most recent epidemiology study was a case-surveillance study during a school outbreak in 2005, which showed that of 104 cases in primary and secondary schools (92 cases were children/adolescents), the attack rate (PCR, culture or serology, cutoff not stated) increased from 4.2% (95% confidence intervals [CI] 0.5%–14.2%) among children aged 5–7 years to 23.8% (95% CI 14.9%–34.6%) among children aged 9 years, decreasing to 18.9% (95% CI 9.4%–32.0%) among children aged 10 years, 9.8% (95% CI 2.7%–23.0%) among children aged 11–19 years and 16.7% (95% CI 8.6%–27.9%) among adults aged ≥ 20 years. The overall attack rate was 15.0% (70/467) [50]. In a study of infected households in Germany between 1992 and 1994, 104 children (85%) and 18 adults (15%) were the source of pertussis. These households consisted of 265 adults (aged 19–83 years), of whom 84 (31%) had laboratory-confirmed pertussis. Of the 84 laboratory-confirmed adult cases, 81% had respiratory symptoms for ≥ 21 days, and compared with children, adults

had fewer episodes of prolonged cough, vomiting and whoop [74].

### *The Netherlands*

In The Netherlands, the NIP includes DTaP at 2, 3, 4 and 11 months, a booster at 4 years (introduced 2005) and TdaP for pregnant women from 22 weeks gestation [34].

National surveillance in The Netherlands shows that pertussis epidemics occur every 2 to 3 years. A serosurvey conducted between 2006 and 2007 of a randomly selected age-stratified sample of 7903 people estimated that about 9% of the population aged > 9 years had had pertussis infection in the past year (PT IgG > 62.5 EU/ml). The percentage was highest in those aged 65–79 years (12%). The overall pertussis seroprevalence had more than doubled compared with a decade earlier. The authors suggest that the increased seroprevalence was consistent with the steady increase in reported clinical cases and hospitalised cases in adolescents and adults in the past decade [63]. An analysis of pertussis hospitalisation and notifications in The Netherlands showed that during 2002–2005, in children aged 1–4 years, the incidences of hospitalisations and notifications, respectively, were 48% and 44% lower than during 1998–2001. Similarly, in children aged 5–9 years, the incidence of hospitalisations and notifications decreased by 32% and 15%, respectively, between the same periods. However, among cohorts aged 10–19, 20–59 and > 60 years, the incidence of notifications increased 60%, 44% and 68%, respectively [60].

### *Luxembourg*

In a small study of migrants arriving in Luxembourg in 2012 ($n$ = 410) the highest seroprevalence (no cutoff stated) was found in those aged 13–20 years (43.8%) and the lowest in those aged 41–50 years (37.5%) [55].

### *The UK*

In the UK, the NIP includes DTaP at 8, 12, 16 weeks and 3 years and aP vaccine for pregnant women from 16 weeks gestation (introduced 2012) [75]. In the UK, infant wP vaccine was used until 2004, when it was replaced with aP vaccine [76].

A UK study of the effectiveness of maternal vaccination against pertussis compared the shift in the percentage of PCR/culture-confirmed cases by age groups between 2008 and 2013, which peaked in October 2012 (1565 cases) and then fell across all age groups [65]. For the first 9 months of 2013 compared with the same period in 2012, the greatest proportionate fall in confirmed cases (328 cases in 2012 vs. 72 cases in 2013, – 78%, 95% CI – 372 to 83) occurred in infants aged < 3 months, although the incidence remained highest in this age group. In non-infant age groups (> 1 year) in the same period, confirmed cases in 2013 fell proportionately less (between 29 and 41%) from 2012 and increased relative to 2011.

Although the numbers reported remained small, cases in adults aged ≥ 20 years were roughly double those in 2012 and more than triple those in 2011 [65]. In a subsequent publication reporting pertussis cases between 2012 and 2015, incidence fell from a peak of 17.6/100,000 in 2012 to 8.6, 6.2 and 7.7/100,000 in 2013, 2014 and 2015, respectively [68]. The overall increase in incidence relative to pre-peak in 2012 was observed in all age groups > 6 months with the combined 3-year comparator periods (2009–2011 vs. 2013–2015) increasing from 1.5 to 3.1/100,000 in those aged 6–11 months (2.1 times higher); 0.7 to 2.2/100,000 in those aged 1–4 years (3.1 times higher); 0.6 to 4.6/100,000 in those aged 5–9 years (7.7 times higher); 2.6 to 13.6/100,000 in those aged 10–14 years (5.2 times higher); 1.1 to 7.4/100,000 in those aged ≥ 15 years (6.7 times higher). The greatest increase was observed in children aged 5–9 years [68].

In a serosurvey in the UK between 1996 and 1997, samples were taken from 356 patients who were diagnosed clinically with acute laryngitis/tracheitis or whooping cough (acute spasmodic cough of three weeks duration). Forty out of 145 who provided specimens for serological testing had evidence of recent infection with *B pertussis* (increased anti-PT IgG levels versus controls). The prevalence among those aged 5–14 years was 45%, and prevalence

declined with increasing age until age > 65 years, when it increased to 22% [73].

## Central and Eastern Europe

An overview of epidemiology studies in Central and Eastern European countries is shown in Table 3. Data were reported from Bulgaria [77–79], Czech Republic [80, 81], Estonia [82, 83], Hungary [84], Poland [85] and Slovenia [86, 87].

### *Poland*

The NIP in Poland mandates DTwP 2, 4, 6 and 16 months and an aP booster at 6 years and 14 years [88]. There were ten studies of pertussis epidemiology in Poland [86, 89–95], including several publications providing annual notified cases in 2005 and 2009 and between 2011 and 2015.

Among 1455 reported pertussis cases between 2005 and 2009, the incidences were highest in two groups: infants aged < 1 year, from 13.3/100,000 in 2006 to 32.7/100,000 in 2007, and children aged 10–14 years, from 11.8/100,000 in 2006 to 68.5/100,000 in 2008. Adolescents aged 10–19 years accounted for 60% of cases and adults aged 20–64 years accounted for 20% of cases. Infants aged < 1 year accounted for only 4% of cases [89].

Population-based, national surveillance showed that in most years between 2010 and 2015 infants and young children were the most affected groups, apart from 2012 when the incidence in older children aged 10–14 years was 56.5/100,000 population and in those aged > 15 years, was 7.8/100,000, with these two age groups accounting for 77% of cases in 2012 compared with 67% in 2010, 73% in 2011, 66% in 2013 and 65.1% in 2014 [86, 89–95]. In 2011, in adolescents aged 10–14 years and those aged > 15 years, the age-adjusted incidences were 20.3/100,000 and 2.5/100,000, respectively. In 2011, half of the cases occurred in people aged > 15 years, while one in three cases in children was in children aged 0–4 years and 5–9 years [92]. The same was observed in 2012 where the majority of cases were in children aged 10–14 years and > 15 years (77%) [93] and in 2013 where the majority of cases occurred in adolescents aged > 15 years (92%) [94]. In 2014, adolescents were still the largest group (46%) but were not the most cases [95].

### *Estonia*

The NIP in Estonia includes DTaP at 3, 4, 6 months and 2 years, a booster at 6–7 years (introduced in 2008) and aP booster dose at 15–17 years (introduced in 2012) [96]. A wP vaccine was used in Estonia until 2008, when it was replaced by an aP vaccine [96].

There were four studies from Estonia, and the most recent was a hospital-based study between 2012 and 2014 including 549 patients with cough ≥ 7 days. There were 22 cases of pertussis (PCR and anti-IgG > 100 IU/ml), of which 5.6% were aged 1–9 years, 6.3% aged 10–17 years, 3.1% aged 18–64 years and none aged ≥ 65 years [96]. Population-based active surveillance of 3327 adults showed that between January and February 2013, 2.7% had anti-PT IgG ≥ 62.5 to < 125 IU/ml and 0.6% had anti-PT IgG ≥ 125 IU/ml [83].

### *Bulgaria*

In Bulgaria, the NIP mandates DTaP at 2, 3, 4 and 16 months (not earlier than 12 months after the 3rd dose) and an aP booster at 6 years and 12 years [34]. A wP vaccine was used in Bulgaria until 2008 when it was replaced with an aP vaccine [78].

Bulgaria had 29 pertussis cases notified between 2009 and 2014, of which 5 were PCR confirmed, and the incidence rate was highest in infants aged < 1 year (12 cases), followed by children aged 0–9 years (9 cases) [78]. In a Bulgarian study of hospitalised children and adolescents, among 28 PCR-confirmed cases between 2009 and 2016, 64% were aged > 1 year and 21% aged 1–3 years, whereas only two cases were aged 10–14 years [77].

### *Slovenia*

The NIP in Slovenia mandates DTaP at 3, 5 and 11–18 months and an aP booster at 8 years. An aP booster dose is recommended for people aged > 65 years and for pregnant women between 28 and 36 weeks gestation [34]. A wP

vaccine was used in Slovenia until 1999, when it was replaced with an aP vaccine [97].

In Slovenia, cyclic outbreaks of pertussis were reported in the 1990s, and between 2003 and 2006, the number of reported cases increased 6.5 times. Based on national surveillance data, after 2003, there was a shift in the age distribution of pertussis cases, and between 2003 and 2005, the rates in adolescents aged 10–14 years increased from 35 to 47% compared with 2% in 1991 [97]. In 2005, in Slovenia for the first time, the highest rates were observed in adolescents rather than infants, and in 2006 the incidence of pertussis was 27.5/100,000 population overall and 220/100,000 population in adolescents aged 10–14 years [97]. Active surveillance of 3418 population-based samples in Slovenia in 2000 showed that the rate of anti-PT IgG > 125 U/ml was 2.3% and anti-PT IgG 62.5 to < 125 U/ml was 6.7% [87].

### *Czech Republic*

The NIP in the Czech Republic mandates DTaP at 3, 5, 11–13 months and an aP booster at 5–6 years and 10–11 years. An aP booster is recommended for those aged > 65 years and for pregnant women between 28 and 36 weeks' gestation, but this is not state funded [34]. In the Czech Republic, infant wP vaccine was used until 2007, when it was replaced with an aP vaccine [98].

Notified cases in the Czech Republic were assessed from 1988 to 2008, and the highest age-specific incidence was observed in adolescents aged 10–14 years, at 79.8/100,000, and most (93.1%) cases were notified in children/adolescents aged 0–19 years. During this period, the peak incidence moved from the youngest and pre-school age groups towards school-aged and older school-aged children [80].

### *Hungary*

In Hungary, the NIP mandates DTaP at 2, 3, 4 and 18 months and an aP booster at 6 years and 11–13 years [34].

There was one study from Hungary which assessed pertussis antibodies in 1999 people in 2014–2015. Overall, 14.8% had anti-PT IgG > 18 EU/ml, 1.1% had anti-PT IgG > 70 EU/ml and 0.1% had a anti-PT IgG > 110 EU/ml. Logistic regression showed a significant relationship between increased rates of seropositivity and age ≥ 60 years (odds ratio [OR], 1.97; 95% CI 1.39–2.80; $p = 0.0002$) or 18–29 years (OR, 1.67; 95% CI 1.13–2.46; p = 0.0094) vs. 45–59 years [84].

## Southern Europe

An overview of epidemiology studies from Southern European countries is shown in Table 4. This included studies from Cyprus [99], Greece [100, 101], Italy [102–110], Portugal [85] and Spain [111–127].

### *Cyprus*

Since 1996, the NIP in Cyprus has included DTaP at 2, 4, 6 and 18 months and at age 4–6 years [99]. In November 2002, pertussis was included in the active surveillance scheme, the Greece & Cyprus Paediatric Surveillance Unit (GCPSU), and the only study from Cyprus identified for the review was a case surveillance study of an outbreak in 2003, including 24 cases with anti-PT IgA antibodies; the incidence was highest in young children ($n = 22$), and the majority of cases were in adolescents ($n = 16$) and adults ($n = 6$). The authors concluded that this confirms the shift in age of pertussis from children to adolescence and adults and that the main factors were waning immunity or incomplete immunisation [99].

### *Greece*

The NIP in Greece includes DTaP 2, 4, 6 and 15–18 months and aP boosters at 4–6 years and 11–12 years and a booster dose in adulthood [34].

In Greece in 2000, among 431 serum samples from healthy subjects aged 1 day to 80 years, IgG antibodies to PT and filamentous haemagglutinin (FHA) were significantly elevated with age (analysis of variance (ANOVA), $p < 0.001$). In addition, a significant increase in antibody levels was detected in adults aged > 50 years compared with children aged 5–10 years (post-hoc Scheffé analysis, $p = 0.007$). These data suggest that pertussis occurs frequently in Greek

adults and that sometimes a fifth booster vaccine dose is not given after the second year of life [101]. In another study in Greece in 2009, based on 373 adults aged 17–65 years, there were three groups: 283 children who were hospitalised with the clinical diagnosis of pertussis, 57 household contacts of 57 children with PCR-confirmed pertussis and 33 adults who suffered from chronic cough. Increased prevalence of pertussis was observed with increasing age [100].

***Italy***

The NIP in Italy involves legally mandated DTaP at 3, 5 and 11 months and an aP booster at 6 years and 12–18 years since 2017. An aP vaccine is recommended for adults, to be given 10 years after the final DTaP vaccination and for pregnant women in the third trimester [34].

A study using the Italian surveillance system tracked the incidence of notified diseases in 371,670 children aged < 15 years in 2002. The highest age-specific incidence rate was observed in children aged 1–4 years for varicella, rubella and measles, in children aged 5–9 years for mumps and in children aged 10–14 years for pertussis (366/100,000) [108]. In a study in Italy conducted between 2013 and 2015, among 168 parents of children with pertussis, 40% were found to have anti-PT IgG ≥ 100 IU/ml. Based on serology, the percentage of pertussis cases that had at least one parent as the source of infection was 49.1%, and when cough symptoms were taken into account, the percentage of parents who could be considered as transmitters of the infection to their infants was 56.4% [105]. In another study of pertussis seroprevalence in Italy, using sera ($n$ = 639) collected between 2012 and 2013 from adults aged 20–29 years and 30–39 years (reproductive age), and ≥ 60 years, the proportion of people with anti-PT IgG > 100 IU/ml increased significantly from 9.3% (95% CI 7.5–11.1%; 96/1037) in 1996–1997 to 14.1% (95% CI 11.4–16.8%; 90/639) in 2012–2013. By age, between 2012 and 2013, the rate of anti-PT IgG > 100 IU/ml was 7.1% for 20–29 years, 3.2% for 30–39 years and 4.6% for ≥ 60 years [106]. A pertussis seroprevalence study of unvaccinated Italian children and adolescents ($n$ = 3875) between 1998 and 1999 reported the overall prevalence of anti-PT IgG antibodies was 80.8% (measured absorbance > 3 times greater than that of negative sera). Prevalence increased with age from 33.5% in those aged 1–3 years to 95% in those aged 17–19 years [102].

***Spain***

In Spain the NIP includes DTaP at 2, 4 and 11 months and an aP booster at 6 years and 12–18 years. An aP booster is recommended for pregnant women from 27 weeks' gestation [34]. A wP vaccine was used up to 2005 when it was replaced with an aP vaccine.

Based on notified cases in Spain, compared with 1998–2001, in 2010–2012, the incidence rate increased notably in all age groups, with incidence rate ratios ranging from 2.5 (95% CI 2.3–2.8) in children aged 5–9 years to 36.0 (95% CI 19.4–66.8) in adults aged 20–29 years [114]. In Spain, between 1997 and 2010, there were 3397 notified cases of pertussis, with an incidence of 54.2/100,000 in infants aged < 1 year, 3.59/100,000 in adolescents aged 10–14 years and 0.1/100,000 in adults aged > 45 years [122]. The results are consistent with Spain's vaccination history and suggest a progressive increase in susceptible individuals due to waning immunity after years of low incidence. Pertussis has been reported to be circulating in healthcare workers (HCWs) in Spain, as reported by a study of 220 HCWs between 2008 and 2010, among which 10.5% has anti-PT IgG > 45–99 - IU/ml and 4.5% had PT IgG > 100 IU/ml [125].

In a Spanish study of sera samples from 1153 'young adults' (aged 19–39 years), collected between 2007 and 2010, those aged 30–34 years (about 47%) had the lowest seroprevalence for *B pertussis* (PT IgG cutoff not stated) followed by an increase in those aged 35–39 years (60%). The 25–29-year-old group had the highest seroprevalence (about 86%) [123].

## MORTALITY

There were 19 studies of pertussis deaths in Europe, including Germany [51, 128], Greece [129], Ireland [130], Italy [107, 131], The Netherlands [132–134], Poland [91], Portugal

[135], Slovenia [97], Spain [136], UK [137–139], Ukraine [140] and pan-Europe [141, 142].

### Mortality Rates

In a study of 79,217 pertussis cases reported to national surveillance systems in 16 European Union (EU) member states between 1989 and 2002, 11 countries collected information on death [141]. Overall, there were 32 deaths recorded, of which 1 was a child aged 5–9 years, 1 was aged > 14 years and 30 were infants aged < 1 year. The mortality rate for infants aged < 1 year was 6.3/1000 births. Most deaths ($n$ = 26) were reported in France, and there were no fatal cases reported in Greece, Iceland, Malta and Switzerland [141]. In a similar study of deaths in the period 1998–2002, in which 16 European countries were included in a common database with data from pertussis cases gathered from routine national surveillance, the combined all-age mortality rate was 0.7/1000 population [142].

In the UK, among 50 deaths between 1980 and 1990, the age range was 30 days to 58 years, and infants aged < 1 year accounted for 74%. The pertussis-related mortality rates were 1/21,000 in children aged 5–14 years and 1/8250 in those aged > 16 years [138].

In Italy, between 1925 and 1994, in an era classified as 'pre-vaccination', the all-age mortality rate for pertussis was 2.4/100,000 population, which fell to zero in the 'post-vaccination era' [131]. In The Netherlands, between 1976 and 1988, there were seven deaths from pertussis, six of which were in children aged < 1 year [132]. In a study of an outbreak at a convent in The Netherlands in 1992, pertussis was diagnosed in 45/75 (60%) retired nuns, of whom 4 died, including 3 who were aged > 75 years [133]. Based upon 995,857 notified cases between 1976 and 2000 in Poland, the number of deaths fell from about 1000 in the 1950s to single cases in the 1980s, with the last death from pertussis reported in 1991, although the ages of the fatal cases are not reported [91].

There were 9 pertussis-related deaths notified between 1970 and 2007 in the former East Germany, 4 of which occurred in elderly adults in 2002, and in the former West Germany during the same period, there were 231 deaths, with mortality gradually decreasing. The last three deaths were reported in an infant in 2001, in an elderly woman in 2005 and in a teenager in 2007 [51]. A small-scale German study of 216 cases of pertussis reported 5 deaths between 1993 and 1996, of which 3 were previously healthy children. Two of the deaths were in children aged 0–6 years ($n$ = 73) and one in an adolescent aged > 9 years ($n$ = 11) [128].

### Case Fatality Rates

Six studies provided case fatality rates in European countries, the most recent of which was a study in Portugal between 2000 and 2015, which showed that among 2281 hospitalised patients with pertussis (aged from birth to 65 years), the overall case fatality rate was 0.7% [135]. The case fatality rate was 11.5% in adults aged 18–64 years and 17.4% in adults aged > 65 years [135]. In another study of patients hospitalised with pertussis in Spain, among 2216 cases recorded between 1995 and 1999, 14 were fatal. Most deaths (71%) were among children aged < 1 year, with two fatal cases in adults [136]. The case fatality rate was higher in people aged > 50 years (28.6%) compared with those aged 1–5 years (1.4%) and 1 year (0.5%) [136].

Based on notifications in the UK, there were 5, 1, 1 and 3 pertussis-related deaths in 2008, 2009, 2010 and 2011, at a case fatality rate of 3.4%, 1.1%, 2.3% and 2.5%, respectively. In the epidemic year 2012, and in 2013, there were ten and two deaths at a case fatality rate of 3.0% and 2.8%, respectively [65].

A study in the Ukraine, using a combination of notification data and the literature (from pre-2000), showed that the overall case fatality rate was 0.163% between 1965 and 1991, rising to 0.183% between 1992 and 2005 and then declining to 0.106% between 2006 and 2015 [140]. In Italy, using national notification data between 1961 and 1994, the case fatality rate was 0–1% [107], and in Ireland between 1980 and 1984, the overall pertussis-related case

fatality rate was 0.08%, of which 83% were aged < 1 year [130].

## DISCUSSION

The most recent European Centre for Disease Prevention and Control (ECDC) estimates of pertussis incidence, based on notifications from 29 European countries, show that the most affected age group is infants and that the population aged ≥ 15 years accounts for about 60% of cases [4]. Although the health status of populations is comparable across Europe, there is wide variation in the incidence of pertussis between countries. For example, in the ECDC report of annual notifications in 2017, Norway had the highest notification rate at 46.1/100,000, followed by The Netherlands (26.4), Germany (20.4) and Denmark (18.7), whereas in Greece, Romania and Hungary, the rate was < 1/100,000 [4]. Robust surveillance systems for notifiable diseases are in place in all European countries, and most European countries report pertussis according to an EU case definition [143]. However, national surveillance systems vary from country to country, including diagnostic techniques and reporting regulations. For example, pertussis reporting was not mandatory in Germany until after 2013, and in France, the hospital-based sentinel surveillance system only includes infants aged < 6 months [143]. In addition, although infant DTP vaccination coverage is high in most European countries, coverage varies, for example, in a study of 16 European countries, the coverage of infant DTP vaccination ranged from 89% in Romania to 98% in Finland and Sweden [144]. Moreover, in some countries infant DTP coverage has historically been lower than ideal (i.e. < 95%), leading to vaccination becoming a legal requirement. In France, for example, coverage with hexavalent (DTaP-HBV-IPV-Hib) vaccine in children aged < 1 year increased from 93% in 2017, to 98% in 2018, after vaccination was mandated [145]. Pertussis vaccination coverage among older children and adult groups is not well documented, and the NIP recommendations for these populations vary considerably between countries [145].

In 2006, the Global Pertussis Initiative (GPI), the Consensus on Pertussis Booster Vaccine in Europe and the US Advisory Committee on Immunization Practices recommended that pertussis vaccination should be expanded to include Tdap booster dose for adolescents and adults [9, 146, 147]. In the US, the introduction Tdap 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 [148, 149]. However, although Tdap vaccines are effective against pertussis in adolescents, three studies in the US showed that protection may be moderate and wane rapidly during 3 years after vaccination [150–152]. However, these studies assessed relative effectiveness, i.e. versus a vaccinated population, rather than absolute effectiveness, i.e. versus a vaccination-naïve population. A meta-analysis of these studies showed that the absolute vaccine effectiveness after boosting was 85%, declining by 11.7% per year, suggesting that booster responses in adolescents were better than previously reported [153]. Several European countries now recommend Tdap for adolescents as a booster or as a catch-up dose, yet there are limited data from Europe on the effect of vaccinating adolescents [34]. France introduced Tdap for adolescents in 1998 and a study published in French reported that among pertussis cases in infants aged < 6 months, the mean age of the contact person/source of infection increased from 19.6 years in 1996 to 31.9 years in 2007 [154]. In Sweden, 10 years after introducing a pre-school booster and a school-leaving booster at age 14–16 years, there was an increase in children with anti-PT IgG > 100 EU/ml, yet in a cross section of adults over the same period, there was a decrease in the proportion with anti-PT IgG levels indicative of natural infection and a lower frequency of pertussis cases. The authors suggested that universal vaccination of children and adolescents in Sweden may have reduced natural exposure and herd immunity in adults [31].

Vaccination of adults is currently recommended in some European countries with the aim of reducing pertussis rates in older people

who may serve as a reservoir for infection, although most countries do not include aP boosters for adults in the NIP [34]. National surveillance generally shows that pertussis is circulating in adolescents and adults in Europe. National surveillance in Denmark showed that in 2013 the incidence/100,000 of pertussis in people aged 30–39 years was 7, aged 40–49 years was 9 and aged ≥ 50 years was 3 compared with 110 in those aged < 1 year [19]. In The Netherlands, between 2002 and 2005, the incidence/100,000 of pertussis in people aged 20–59 years was 15.7, and among those aged ≥ 60 years was 11.7, compared with 132.3 in infants aged < 5 months [60]. There are limited data on the effect of vaccinating adults; however, after the introduction of Tdap for adults aged 25–39 years in Paris, the incidence of pertussis in adults decreased from 884/100,000 in 1999–2000 to 145/100,000 in 2008–2009 [155].

Vaccination during pregnancy is a primary prevention strategy to reduce the risk of pertussis infection in unvaccinated and partly vaccinated infants [9, 156]. Pregnant women should be targeted because as well as reducing the risk of mother-to-infant infection, maternal Tdap vaccination is reported to induce high levels of transplacental antibodies that can protect the newborn [157]. Isolating vulnerable infants from contacts that could transmit infection (cocooning) is also a way to reduce the risk of transmission, although the effectiveness of the strategy is associated with the proportion of contacts that are vaccinated, i.e. parents and siblings [158, 159]. Therefore, the GPI strongly recommends the use of aP vaccine in pregnant women and also encourages booster doses in adolescents [159]. Several European countries currently recommend aP vaccine for pregnant women on the NIP, including Belgium, Czech Republic, Denmark, Ireland, Italy, The Netherlands, Slovenia, Spain and the UK [160].

All European countries have included infant DTP vaccination in the NIP for > 30 years, and apart from Poland, all countries have replaced infant wP vaccine with infant aP vaccine. Acellular pertussis vaccines contain inactivated pertussis toxin (PT) and may contain one or more other bacterial components such as filamentous haemagglutinin (FHA), pertactin (Pn) and fimbriae (FIM) types 2 and 3. It is still unclear how other antigens than PT contribute to the protective effect of vaccines. Clinical and real-world studies show that all licensed pertussis vaccines are highly protective against pertussis and differences in protection among pertussis vaccines based on antigen number have not been confirmed [161]. A pre-school/early school booster dose was introduced in most European countries circa 2003–2010, and currently all countries apart from Malta include a pre-school/early school booster dose [34]. Following guidance from the Consensus on Pertussis Booster Vaccination in Europe (COPE) group, in 2009, several countries introduced booster doses for adolescents. However, European countries that currently do not include an adolescent booster dose in the NIP include Denmark, The Netherlands, the UK, Romania, Spain and Portugal [34]. Currently, at least one booster dose of aP vaccine for adults is included in the NIP in Austria, Belgium, Liechtenstein, Germany, Iceland (individuals at risk) and Luxemburg [34].

Most of the studies identified that reported pertussis-related deaths in Europe did not include the epidemic outbreak in 2012. Based on notifications in Europe in 1998–2002, the overall pertussis-related mortality rate was 0.7/1000, and in 1989–2002, there were 30 deaths in infants aged < 1 year, 1 death in a school-aged child and 1 death in an adolescent [141]. Although the mortality rates in adults are extremely low, the reported case fatality rates for adults hospitalised for pertussis are relatively high. In a study in Portugal in 2000–2015, among adults aged 18–64 years hospitalised with pertussis, the case fatality rate was 11.5%, increasing to 17.4% in those aged > 65 years [135]. In a similar study in Spain in 1995, the case fatality rate was 28.6% in adults aged > 50 years compared with only 1.4% and 0.5% in children aged 1–5 years and 1 year, respectively [135]. Indeed, although pertussis disease is often mild in adults, data from Australia suggest that elderly people, particularly those with respiratory co-morbid conditions, are at a greater risk of pertussis-related hospitalisation and death than younger adults [162]. Interestingly, during an outbreak in a convent

in The Netherlands in 1992 in which four nuns died, the incidence of pertussis increased with the time that the nuns had spent in isolation, but did not increase with age. Pertussis was confirmed in 2/24 (8%) staff members and 45/75 (60%) nuns (unvaccinated), and most of the nuns had been retired and isolated in the convent for between 35 and 70 years, but had had a career outside the convent. There were nine nuns with a career entirely inside the convent, and all of them were positive for pertussis [56].

The real incidence of pertussis in Europe is likely to be much higher than that captured by surveillance systems; in particular, pertussis in adolescents and adults is likely to be underreported [9, 163]. Pertussis is known to be underdiagnosed in adults partly because the public and HCWs often regard pertussis as a childhood disease so that it is not considered, and also because pertussis is difficult to discern from other acute cough syndromes in adults [11, 164]. Indeed, as well as increasing pertussis vaccination coverage in adolescents, adults and pregnant women in European countries, mitigation strategies should include improved diagnosis and treatment in lower risk populations.

The main limitation of this review is that it provides a narrative analysis of studies that differed widely in terms of pertussis surveillance and notification, case definitions and diagnostic methods as well as a lack of global consensus on anti-PT IgG antibody cutoffs. In addition, the review does not include non-English language publications, which might have excluded some studies that would have provided relevant data. However, the strength of the review was the use of the well-established technique of a systematic review to provide a comprehensive overview of pertussis in older children and adults in Europe.

## CONCLUSIONS

Whereas infants and young children are routinely vaccinated against pertussis in European countries, few countries provide booster doses for adolescents and adults, suggesting that vaccine coverage among these groups across Europe is relatively low. Numerous studies show that pertussis is circulating among adults in Europe, yet active surveillance suggests that national surveillance likely underestimates the incidence of pertussis among older groups. As well as weaknesses in surveillance among older populations, low awareness among the public and among HCWs means that pertussis is likely underdiagnosed in European countries. Improved awareness and reporting systems are needed to help define the true burden of pertussis in older populations and their role in disease transmission.

## ACKNOWLEDGEMENTS

***Funding.*** Sponsorship for this study and the rapid service fees for the journal were funded by Sanofi Pasteur, France.

***Editorial Assistance.*** The authors acknowledge Annick Moon of inScience Communications, Springer Healthcare Ltd, Chester, UK, for editorial assistance with the preparation of this manuscript. This assistance was funded by Sanofi Pasteur. The authors also thank Burnedette Rose-Hill for editorial assistance and manuscript coordination on behalf of Sanofi Pasteur.

***Authorship.*** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

***Authorship contributions.*** Denis Macina: Conceptualization, methodology, investigation, Writing—review and editing. Keith Evans: Methodology, investigation, Writing—review and editing.

***Disclosures.*** Denis Macina is an employee of Sanofi Pasteur and may hold shares and/or stock options in the company. Keith Evans was provided with funding by Sanofi Pasteur to conduct

the literature review in collaboration with Denis Macina.

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

***Data availability.*** Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.



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