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REVIEW ARTICLE

Asymptomatic Infection and Transmission of Pertussis in Households: A Systematic Review

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We conducted a systematic review to describe the frequency of mild, atypical, and asymptomatic infection among household contacts of pertussis cases and to explore the published literature for evidence of asymptomatic transmission. We included studies that obtained and tested laboratory specimens from household contacts regardless of symptom presentation and reported the proportion of cases with typical, mild/atypical, or asymptomatic infection. After screening 6789 articles, we included 26 studies. Fourteen studies reported household contacts with mild/atypical pertussis. These comprised up to 46.2% of all contacts tested. Twenty-four studies reported asymptomatic contacts with laboratory-confirmed pertussis, comprising up to 55.6% of those tested. Seven studies presented evidence consistent with asymptomatic pertussis transmission between household contacts. Our results demonstrate a high prevalence of subclinical infection in household contacts of pertussis cases, which may play a substantial role in the ongoing transmission of disease. Our review reveals a gap in our understanding of pertussis transmission.

Keywords. pertussis; polymerase chain reaction; asymptomatic; atypical; contacts.

Many countries have experienced a resurgence of pertussis over the last 20–30 years [1, 2], hypothesized to stem from a variety of factors including vaccine-driven selection [3], increased disease awareness and testing [1, 4], improved diagnostics [4], and waning immunity [5].

Pertussis resurgence has been particularly noted in jurisdictions that have adopted acellular pertussis (aP) vaccines in place of whole-cell (wP) vaccines [1]. While safer and less reactogenic, aP vaccines elicit a mismatched immune response and decreased duration of protection compared to wP vaccines and naturally acquired immunity [6]. Utilizing a baboon model of infection, Warfel and colleagues found that both wP and aP vaccines protected against severe disease, but neither prevented infection [7]. When challenged, aP-vaccinated baboons were colonized for twice as long as wP-vaccinated baboons and transmitted pertussis to naive contacts [7]. These findings suggest that vaccinated individuals may harbor and transmit the infection, even in the absence of typical pertussis symptoms [7, 8]. Mild/atypical and asymptomatic infection may therefore play an important role in transmission dynamics and ongoing pertussis circulation and resurgence [7, 8], particularly since the switch to aP vaccine in many countries. However, to our knowledge the extent of mild and asymptomatic infection in humans has not been systematically investigated.

We undertook this systematic review to describe the frequency of mild/atypical and asymptomatic *Bordetella pertussis* infection and evidence of asymptomatic transmission.

METHODS

Search and Screening Strategy

We searched MEDLINE, Embase, CINAHL, BIOSIS Previews, Scopus, and CENTRAL databases (Supplementary Materials) on 12 May 2016. An updated search was completed on 17 October 2018. No date or language limits were set.

We completed title and abstract screening and full-text review in duplicate. To proceed to full-text review, the title or abstract was required to contain the words "pertussis" or "whooping cough" and needed to describe either familial or household relationships or a household or household-like setting. All studies passed by at least 1 reviewer were included for full-text review.

For inclusion after full-text review, we required that each study document household exposure to a laboratory-confirmed pertussis case, collect and test specimens from household contacts regardless of symptoms, and report the number

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or proportion of laboratory-confirmed cases and contacts with typical, mild/atypical, or asymptomatic pertussis infection. We excluded studies that only tested household contacts with respiratory symptoms. When laboratory-confirmed and epidemiologically linked cases were reported together, we attempted to contact the study authors to determine which cases were laboratory-confirmed.

We reviewed studies published in English in duplicate (R. C. and E. K., C. A. and L. F.) and resolved all discrepancies through consensus with a third reviewer (S. B., R. C.). Where possible, studies published in other languages were also screened and abstracted, including those in French (N. C.), Spanish (M. F.), Hebrew (S. B.), Dutch (H. M.), Italian (K. K.), and German (K. K.).

Data Abstraction

We abstracted all data in duplicate, including case definitions, laboratory methods, vaccine history, the number of cases and types of symptoms, and potential determinants for transmission. Discrepancies were resolved through consensus.

Defining Asymptomatic, Mild or Atypical, and Typical Pertussis

To classify pertussis cases as asymptomatic, mild/atypical, or typical, we utilized case definitions that capture a continuum of disease severity (Table 1) [9–11].

We required laboratory confirmation for inclusion as a pertussis case and accepted all laboratory methods to confirm infection. We limited the case definition for asymptomatic pertussis to laboratory-confirmed infection in the absence of clinical symptoms, while being mindful that asymptomatic pertussis may be conceptualized as detection, colonization, or immune boosting.

Evidence of Asymptomatic Transmission

We considered all evidence that provided temporal information to determine the relative order of pertussis infection within the household unit, including the timing of symptom onset (if symptomatic) and the timing of laboratory-positive tests among contacts and in relation to the index case. We also considered differences in test sensitivity between culture, polymerase chain reaction (PCR), and serology dependent on the time elapsed between testing and infection [12]. Other evidence considered included the identification of household units where all infected contacts of infant index cases were asymptomatic, as immediate family members have been established as the primary source of infection for infant cases of pertussis [13].

Data Analyses

Meta-analysis was not conducted due to study heterogeneity. Instead, we present ranges of the proportion of household contacts with laboratory-confirmed pertussis stratified by symptom classification. For individual study estimates, 95% confidence intervals were constructed from reported data using the Clopper-Pearson method.

Quality Appraisal

Two reviewers (R. C. and E. K.) independently assessed the quality of evidence of all studies included for data abstraction using the Meta Quality Appraisal Tool [14], focusing on factors that may impact the detection and confirmation of infection, including laboratory methods, timing and type of specimen collection, and the proportion of household contacts tested (Supplementary Materials).

RESULTS

Our search retrieved 6789 unique articles (Figure 1). We selected 292 for full-text review and included 25 articles for data abstraction and quality appraisal [11, 15–38]. We attempted to contact the authors of 14 additional studies where epidemiologically linked and laboratory-confirmed index cases or contacts were reported together. Only 1 author provided relevant data [39], bringing the number of included articles to 26. The most frequent reason for exclusion during full-text review was that the symptoms of contacts were not described.

Table 1. Case Definitions

Classification	Definition
Typical pertussis [9, 10]	Laboratory-confirmed *Bordetella pertussis* infection with cough illness lasting ≥2 weeks with at least 1 of the following signs or symptoms: • paroxysms of coughing, • inspiratory whoop, • posttussive vomiting, • apnea with or without cyanosis (for infants aged <1 year only).
Symptomatic pertussis	Laboratory-confirmed *B. pertussis* infection where symptoms were reported but typical and mild/atypical pertussis were not differentiated.
Mild/atypical pertussis	Acute cough illness of any duration with laboratory-confirmed *B. pertussis* infection that does not meet the case definition for typical or asymptomatic infection.
Nontypical pertussis	Laboratory-confirmed *B. pertussis* infection where asymptomatic and mild/atypical pertussis cases were reported together.
Asymptomatic pertussis [11]	Laboratory-confirmed *B. pertussis* infection in a person without any cough or cold symptoms.
Asymptomatic transmission	Transmission of *B. pertussis* from a person with a laboratory-confirmed, asymptomatic pertussis infection to another individual with laboratory-confirmed infection.

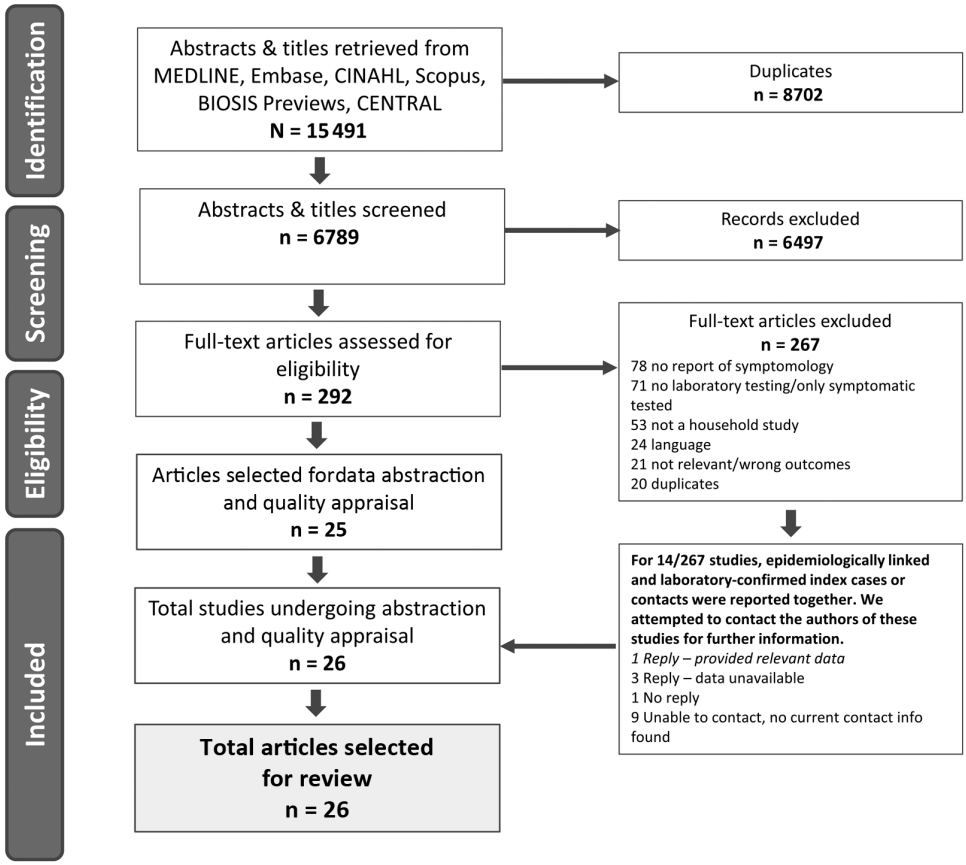

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram.

The 26 articles included 23 descriptive studies [11, 15–17, 20–33, 35–39], 2 case reports [18, 34], and 1 conference abstract [19]. Studies were conducted between 1979 and 2015. Twenty-one studies were conducted in household settings [11, 17–26, 28–35, 37, 39] and 5 occurred in congregate living environments [15, 16, 27, 36, 38] (Table 2). Sixteen studies prospectively followed contacts for incident infection or the emergence of symptoms, or both [11, 15–18, 21, 23–25, 27, 28, 30, 31, 36–38], while 10 utilized a single-visit, cross-sectional design [19, 20, 22, 26, 29, 32–35, 39]. In only 5 studies were all household contacts tested [16, 23, 27, 30, 38]. In 9 studies the authors were unable to test all contacts [11, 15, 17, 19, 25, 31, 32, 36, 37], and in the remaining 12 it was unclear whether all household contacts were tested [18, 20–22, 24, 26, 28, 29, 33–35, 39].

A mix of bacterial culture, direct fluorescent antibody, PCR, and serology were used for diagnosis of *B. pertussis* infection. In 10 studies the type of vaccine study participants had received was not reported or was unclear [17–19, 24–26, 34, 35, 37, 39]. In 11 studies the participants had received wP vaccine [15, 20–22, 27, 28, 30–32, 36, 38], in 3 studies they had received aP vaccine [11, 16, 29], and in 2 studies participants had received either wP or aP vaccines or a combination of the 2 [23, 33]. However, reported vaccination history was rarely verified. Chemoprophylaxis was offered to household contacts in 12 studies [15–17, 19, 20, 22, 23, 27, 30, 31, 36, 38], although treatment uptake and timing were not well described.

Pertussis Infection in Household Contacts

The proportion of tested contacts with laboratory-confirmed pertussis ranged from 8% (28/351) [20] to 83% (15/18) [30], excluding 2 studies where the total number of tested contacts was not reported (Table 3) [18, 21].

Of the 26 studies, 1 reported a laboratory-positive contact with mild symptoms but failed to report the symptoms of other contacts or the total number of contacts tested; that study was eliminated from further analysis [18]. In the remaining 25 studies, some reported laboratory-confirmed typical, mild/atypical, and asymptomatic contact cases as distinct groups, while others grouped similar symptom classifications together (Figure 2).

Fifteen of 25 studies reported the laboratory results of household contacts with typical pertussis symptoms as a distinct group (Figure 3A). Of these, the proportion of laboratory-confirmed contacts with typical disease ranged from 0% (0/29)

Table 2. Characteristics of Included Studies

Characteristic	Number of Studies (N = 26) n (%)
Language	
English	22 (84.6)
Spanish	3 (11.5)
French	1 (3.8)
Study country	
Canada	1 (3.8)
United States	5 (19.2)
United Kingdom	2 (7.7)
France	4 (15.4)
Finland	1 (3.8)
Sweden	1 (3.8)
Japan	3 (11.5)
Mexico	2 (7.7)
Chile	1 (3.8)
Italy	1 (3.8)
Belgium	1 (3.8)
The Netherlands	1 (3.8)
Brazil	1 (3.8)
Turkey	1 (3.8)
France, Germany, United States, Canada	1 (3.8)
Study setting	
Household	21 (80.8)
Household-like communal residence	5 (19.2)
Study type	
Prospective	16 (61.5)
Cross-sectional	10 (38.5)
Proportion of household contacts tested	
All household contacts	5 (19.2)
Some household contacts	9 (34.6)
Unknown	12 (46.2)
Age criteria for laboratory testing	
Adults only	5 (19.2)
Children only	1 (3.8)
Both adults and children	20 (76.9)
Laboratory methods	
Polymerase chain reaction only	3 (11.5)
Cell culture only	1 (3.8)
Serology only	0 (0)
Direct fluorescent antibody only	0 (0)
Multiple methods	22 (84.6)
Vaccine type of cases and contacts	
wP	11 (42.3)
aP	3 (11.5)
Combination of wP and aP	2 (7.7)
Not reported/unclear	10 (38.5)
Reported symptom classification for contacts	
Asymptomatic, mild/atypical, typical	14 (53.8)
Asymptomatic, symptomatic	10 (38.5)
Nontypical, typical	1 (3.8)
Mild only	1 (3.8)

Abbreviations: aP, acellular pertussis vaccine; wP, whole-cell pertussis vaccine.

[35] to 56% (28/50) [38] of all contacts tested. An additional 10 studies grouped all symptomatic contacts together, without differentiating typical from mild/atypical symptoms (Figure 3B). The proportion of all laboratory-confirmed contacts with symptomatic disease ranged from 3% (11/351) [20] to 45% (34/76) [31].

Fourteen studies reported mild or atypical infection in household contacts separately from asymptomatic and typical pertussis (Figure 3C). In these, the proportion of contacts with mild or atypical infection ranged from 3% (3/101) [15] to 46% (12/26) [32] of all contacts tested.

Of the 25 studies included in this analysis, 24 reported asymptomatic cases as a distinct group. The proportion of laboratory-confirmed contacts with asymptomatic infection ranged from 5% (17/351) [20] to 56% (10/18) [30] of all contacts tested (Figure 3D). In the remaining study, the authors did not differentiate asymptomatic and mild/atypical pertussis [38].

Asymptomatic Transmission

We identified evidence suggestive of asymptomatic transmission in 7 household studies [11, 24, 26, 28–30, 39]. In 2 [28, 30], the presence and timing of seroconversion in asymptomatic contacts relative to the index cases suggest the possibility of asymptomatic transmission. In the study by Long et al [30], 83% (15/18) of household contacts had laboratory-confirmed pertussis infection by single-sera diagnosis. At the time of index case diagnosis, all 15 laboratory-positive contacts (10 asymptomatic cases and 5 symptomatic cases) had serological evidence of pertussis infection whereas none of the index cases were seropositive, suggesting that the index cases became infected after their contacts. In addition, 7 of 10 contacts with asymptomatic infection and 3 of 5 contacts with symptomatic infection also had secretory immunoglobulin A antibody detected at the time of index case diagnosis. Similarly, Grimprel et al [28] identified 4 mothers with asymptomatic, laboratory-confirmed pertussis who had seroconverted by the time of infant index case diagnosis. All index case infants were PCR- or culture- positive and only 1 had seroconverted at this time.

In each of the other 5 studies, the authors identified households where all contacts tested had laboratory-confirmed asymptomatic infection [11, 24, 26, 29, 39]. In these households where the index case was often an infant, pertussis was likely transmitted from an asymptomatic household contact to the index case. However, it was often not possible to draw absolute conclusions regarding the direction of transmission. Aside from the study by Kara et al, in which all contacts within 1 household (of 63 studied) were tested and all had asymptomatic laboratory-confirmed pertussis infection [29], most studies were unable to test all household members. Although all tested contacts in the other 4 studies had laboratory-confirmed asymptomatic infection, it is possible that untested, symptomatic household or nonhousehold contacts transmitted the infection to the index case. Notably, De Schutter et al [24] identified 13/18 (72%) households where all household contacts tested had asymptomatic pertussis infection. Using pulsed-field gel electrophoresis

Table 3. Data Abstraction Table

Author (year)	Country	Study Design	Laboratory Method	Specimen Type	Vaccine Type	Post-Exposure Prophylaxis Offered?	Residence Type	Index Cases (N)	Proportion of Contacts Tested, n/N (%)	Proportion With Asymptomatic Pertussis, n/N (%)	Proportion With Mild/Atypical Pertussis, n/N (%)	Proportion With Typical Pertussis, n/N (%)	Proportion With Symptomatic[a] Pertussis, n/N (%)	Proportion With Nontypical[b] Pertussis, n/N (%)	Proportion With Pertussis (total), n/N (%)
Addiss et al (1991) [15]	United States	Prospective	Culture, DFA, serology	NP swab, paired sera, single sera	wP, vaccination status not queried (residents assumed to have had natural infection)	Y	Congregate living	4	101/103 (98.1)	29/101 (28.7)	3/101 (3.0)	2/101 (2.0)	n/a	n/a	34/101 (33.7)
Aoyama et al (1993) [16]	Japan	Prospective	Culture, serology	NP swab, paired sera	aP, (children vaccinated with aP)	Y	Congregate living	1	19/19 (100.0)	6/19 (31.6)	2/19 (10.5)	7/19 (36.8)	n/a	n/a	15/19 (78.9)
Aoyama et al (1992) [17]	Japan	Prospective	Culture, serology	NP swab, paired sera, single sera	NR	Y	Household	89	99/203 (48.8)	9/99 (9.1)	8/99 (8.1)	19/99 (19.2)	n/a	n/a	36/99 (36.4)
Armangil et al (2010) [18]	Turkey	Prospective	Culture, PCR, serology	Single sera	NR	NR	Household	1	Unk	Unk	1/Unk (Unk)	Unk	Unk	Unk	1/Unk (Unk)
Armengaud et al (2005) [19]	France	Cross-sectional	Culture, PCR, serology	NR	NR	Y	Household	34	80/90 (88.9)	18/80 (22.5)	n/a	n/a	18/80 (22.5)	n/a	36/80 (45.0)
Berezin et al (2014) [20]	Brazil	Cross-sectional	Culture, PCR	NP swab	wP	Y	Household	97	351/Unk (Unk)	17/351 (4.8)	n/a	n/a	11/351 (3.1)	n/a	28/351 (8.0)
Bortolussi et al (1995) [21]	Canada	Prospective	Culture	NP aspirate	wP	NR	Household	189	Unk	24/Unk (Unk)	10/Unk (Unk)	14/Unk (Unk)	n/a	n/a	48/Unk (Unk)
Bosdure et al (2008) [22]	France	Cross-sectional	PCR, serology (semiquantitative immunoblot)	NP aspirate (child), NP swab (adult), paired sera	wP	Y	Household	46	134/Unk (Unk)	25/134 (18.7)	29/134 (21.6)	2/134 (1.5)	n/a	n/a	56/134 (41.8)
Crowcroft (2005) [39]	United Kingdom	Cross-sectional	Culture, PCR, serology	NP aspirate (index), paired sera (index), NP swab (contacts), single sera (contacts)	NR	NR	Household	24	54/Unk (Unk)	4/54 (7.4)	n/a	n/a	14/54 (25.9)	n/a	18/54 (33.3)
Deen et al (1995) [25]	United States	Prospective	Culture, DFA, serology	NP swab	NR	NR	Household	0[c]	255/298 (85.6)	52/255 (20.4)	23/255 (9.0)	70/255 (27.5)	n/a	n/a	145/255 (56.9)
de Greeff et al (2010) [23]	The Netherlands	Prospective	Culture, PCR, serology	NP swab	wP: contacts >3 y, aP: contacts ≤3 y	Y	Household	164	560/560 (100.0)	42/560 (7.5)	98/560 (17.5)	159/560 (28.4)	n/a	n/a	299/560 (53.4)
De Schutter et al (2003) [24]	Belgium	Prospective	Culture, PCR	NP aspirate (mostly), NP swab, throat swab, bronchoalveolar lavage	NR	NR	Household	28	63/Unk (Unk)	19/63 (30.2)	4/63 (6.3)	2/63 (3.2)	n/a	n/a	25/63 (39.7)
Fedele et al (2017) [26]	Italy	Cross-sectional	PCR (index only), serology (contacts)	Single sera	Unclear, aP: infants and adults, wP: adults born before 1995	NR	Household	55	74/Unk (Unk)	15/74 (20.3)	n/a	n/a	14/74 (18.9)	n/a	29/74 (39.2)
Fisher et al (1989) [27]	United States	Prospective	Culture, DFA, serology	NP swab	wP	Y	Congregate living	0[c]	66/66 (100.0)	32/66 (48.5)	n/a	n/a	12/66 (18.2)	n/a	44/66 (66.7)
Grimprel et al (1997) [28]	France	Prospective	Culture, PCR (Southern blot), serology (semiquantitative immunoblot)	NP aspirate, prepartum serum, paired sera	wP	NR	Household	28	28/Unk (Unk)	5/28 (17.9)	7/28 (25.0)	9/28 (32.1)	n/a	n/a	21/28 (75.0)

Table 3. Continued

Author (year)	Country	Study Design	Laboratory Method	Specimen Type	Vaccine Type	Post-Exposure Prophylaxis Offered?	Residence Type	Index Cases (N)	Proportion of Contacts Tested, n/N (%)	Proportion With Asymptomatic Pertussis, n/N (%)	Proportion With Mild/Atypical Pertussis, n/N (%)	Proportion With Typical Pertussis, n/N (%)	Proportion With Symptomatic[a] Pertussis, n/N (%)	Proportion With Nontypical[b] Pertussis, n/N (%)	Proportion With Pertussis (total), n/N (%)
Kara et al (2017) [29]	United Kingdom	Cross-sectional	Culture (index only), PCR (index only), oral fluid enzyme-linked immunosorbent assay (contacts)	Oral fluid	aP (primarily)	NR	Household	63	220/Unk (Unk)	31/220 (14.1)	n/a	n/a	66/220 (30.0)	n/a	97/220 (44.1)
Long et al (1990) [30]	United States	Prospective	Culture, DFA, serology	NP swab, NP aspirate, paired sera	wP	Y	Household	4	18/18 (100.0)	10/18 (55.6)	n/a	n/a	5/18 (27.8)	n/a	15/18 (83.3)
Mertsola et al (1983) [31]	Finland	Prospective	Culture, serology	NP swab, paired sera	wP	Y	Household	21	76/78 (97.4)	29/76 (38.2)	n/a	n/a	34/76 (44.7)	n/a	63/76 (82.9)
Perret et al (2011) [32]	Chile	Cross-sectional	PCR	NP swab	wP	NR	Household	10	26/50 (52.0)	4/26 (15.4)	12/26 (46.2)	2/26 (7.7)	n/a	n/a	18/26 (69.2)
Raymond et al (2007) [33]	France	Cross-sectional	PCR	NP aspirate (child), NP swab (adult)	aP: infants, wP: contacts	NR	Household	16	41/Unk (Unk)	4/41 (9.8)	14/41 (34.1)	1/41 (2.4)	n/a	n/a	19/41 (46.3)
Romero-Quechol et al (2007) [34]	Mexico	Cross-sectional	Culture, PCR	NP swab	NR	NR	Household	1	20/Unk (Unk)	2/20 (10.0)	2/20 (10.0)	3/20 (15.0)	n/a	n/a	7/20 (35.0)
Sandoval et al (2008) [35]	Mexico	Cross-sectional	PCR	NP swab	Unclear	NR	Household	7	29/Unk (Unk)	3/29 (10.3)	5/29 (17.2)	0/29 (0.0)	n/a	n/a	8/29 (27.6)
Steketee et al (1988) [36]	United States	Prospective	Culture, DFA, serology	NP swab, paired sera	wP	Y	Congregate living	0[c]	255/278 (91.7)	21/255 (8.2)	n/a	n/a	86/255 (33.7)	n/a	107/255 (42.0)
Storsaeter et al (2003) [37]	Sweden	Prospective	Culture, serology	NP aspirate (index), NP swab (contacts), paired sera	wP or aP: index, Unk: contacts	NR	Household	317	664/808 (82.2)	119/664 (17.9)	76/664 (11.4)	77/664 (11.6)	n/a	n/a	272/664 (41.0)
Tanaka et al (1991) [38]	Japan	Prospective	Culture, serology	NP (method not described), paired sera	wP	Y	Congregate living	0[c]	50/50 (100.0)	n/a	n/a	28/50 (56.0)	n/a	13/50 (26.0)	41/50 (82.0)
Wendelboe et al (2007) [11]	France, Germany, United States, Canada	Prospective	PCR, serology	NP aspirate, NP swab, aired sera	aP	NR	Household	92	347/404 (85.9)	44/347 (12.7)	n/a	n/a	136/347 (39.2%)	n/a	180/347 (51.9)

Abbreviations: aP, acellular pertussis vaccine; DFA, direct fluorescent antibody; n/a, not applicable; NP, nasopharyngeal; NR, not reported; PCR, polymerase chain reaction; Unk, unknown; wP, whole-cell pertussis vaccine.

[a]Laboratory-confirmed *Bordetella pertussis* infection where symptoms were reported, but typical and mild/atypical pertussis were not differentiated.

[b]Laboratory-confirmed *B. pertussis* infection where asymptomatic and mild/atypical pertussis cases were reported together.

[c]Outbreak investigations began after numerous laboratory-confirmed cases were identified.

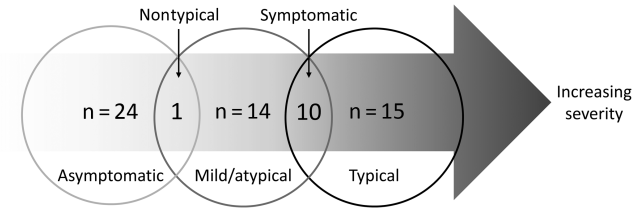

Figure 2. Number of studies reporting pertussis cases by symptom classification. Fifteen studies reported typical symptoms as a distinct category, 14 reported mild/atypical symptoms as a distinct category, 24 reported asymptomatic presentation as a distinct category, 10 reported all symptomatic contacts together, and 1 reported mild/atypical and asymptomatic cases together. This figure excludes a case study where there was insufficient information to determine how cases were classified.

(PFGE), cultured isolates were indistinguishable within households despite variability of PFGE profiles outside of the household unit, further suggesting that transmission likely occurred within the household from an asymptomatic contact to the index case.

Determinants of Pertussis Transmission in Households

Potential determinants of household pertussis transmission were rarely described. We found that there were many potential sources of infection within the household, regardless of their age or relationship to the index case [26, 29]. Additionally, we found that symptoms may not be a prerequisite for pertussis transmission. The large proportion of asymptomatic infection identified in household contacts and the identification of households where all contacts were asymptomatic or had asymptomatic infection may suggest that asymptomatic cases can transmit pertussis [11, 24, 26, 28–30, 40].

The impact of vaccination on infection was not commonly reported. In 2 studies there were apparent trends of increased attack rate with increased time since vaccination with wP vaccine [15, 36]. Three studies also reported that the number of doses of wP vaccine had a limited effect on the occurrence of infection [30, 36, 38]. Similarly, the effects of vaccination on disease presentation were only reported in 6 of 26 studies. While 3 studies found that vaccination did not affect clinical presentation [27, 34, 38], another 3 studies reported an apparent protective effect against severe clinical illness but not infection [16, 24, 30]. However, vaccination history was only verified in 1 study [16], and there was limited reporting of how vaccination history was obtained in the other 5 studies.

None of the studies included in our review explored the role of symptoms on the secondary attack rate.

DISCUSSION

The studies included in this review report a high incidence of asymptomatic and mild/atypical infection among household contacts of pertussis cases. Contacts with laboratory-confirmed asymptomatic or mild/atypical disease frequently formed the majority of household cases, suggesting that individuals with typical symptoms may represent only a small proportion of total pertussis cases. Although the concept of atypical or asymptomatic pertussis infection is far from new [41], the development of more sensitive diagnostics, new animal models [7], and modeling and epidemiological studies [8, 42] have precipitated a greater focus on the contribution of these cases to pertussis transmission dynamics and the overall burden of disease.

Evidence of asymptomatic pertussis transmission has been elusive. In humans, surveillance data often exclude mild and subclinical disease due to the absence of clinical suspicion and the use of case definitions associated with traditional manifestations of clinical pertussis [41]. However, our results demonstrate that there is a high prevalence of infection among close contacts of identified index cases that remains undiagnosed and uncounted. Such infections may play a prominent role in the circulation of disease. Despite limited direct evidence of pertussis transmission from asymptomatic individuals, we identified 7 studies with indirect evidence, including temporal differences in the timing of seroconversion and the identification of household units where all contacts tested had asymptomatic infection. These data signal a likely direction of transmission from asymptomatic contacts to the index case. Indirect evidence of asymptomatic transmission has also been found in other studies. Althouse and Scarpino recently analyzed incidence rates of pertussis in the United States and the United Kingdom and completed a phylodynamic analysis of *B. pertussis* isolates from the United States [8]. Concordant with our findings, they found that the changes in incidence rates in the United States and the United Kingdom and the observed genetic diversity of *B. pertussis* in the United States are consistent with asymptomatic transmission and that this provides the most parsimonious explanation of the resurgence of pertussis.

In our review, only 5 of the included studies tested every household contact. Therefore, the proportions reported here may be underestimates of the true incidence of asymptomatic, mild, and atypical pertussis infection. Testing every pertussis contact within a household is often not feasible, and some study designs such as cross-sectional surveys are not amenable to testing contacts who are not immediately available. Even when investigators succeed in testing every contact, sampling often occurs weeks after the onset of symptoms in the index case when laboratory tests may have reduced sensitivity.

It was difficult to assess the determinants of pertussis infection and transmission from the included studies, largely due to an inability to conclusively identify the source of infection. Additionally, there was limited reporting of vaccination or prior exposure history of cases and contacts, resulting in limited insight into the effects of vaccination on infection and transmission. Nevertheless, it was apparent that pertussis infections

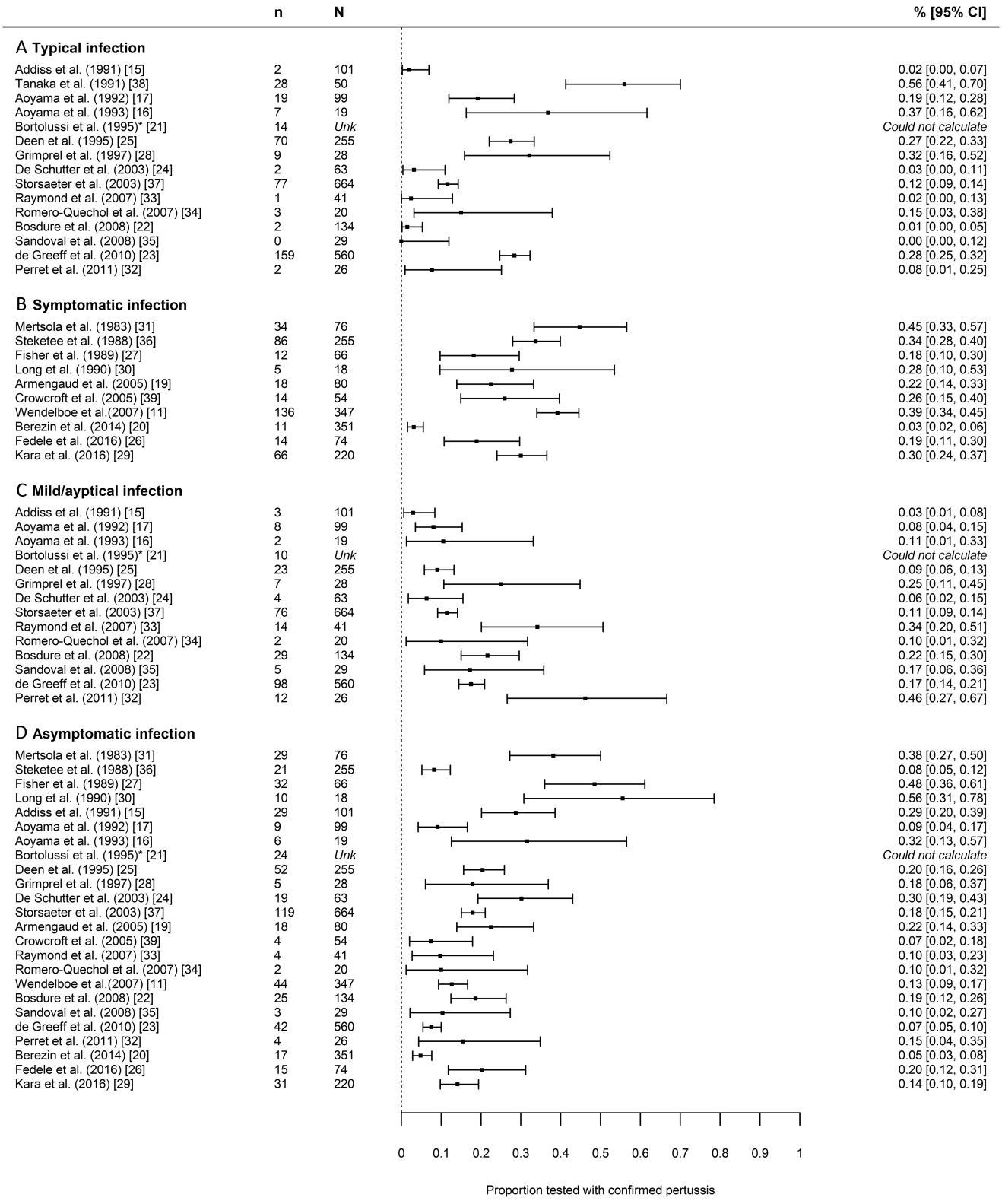

Figure 3. Proportion of contacts tested with (*A*) typical infection, (*B*) symptomatic infection, (*C*) mild/atypical infection, and (*D*) asymptomatic infection. Abbreviation: CI, confidence interval.

occurred in recipients of both wP and aP vaccines. Importantly, cell-mediated immunity, which appears to be essential for bacterial clearance and may be a key component for protection from infection, was not assessed [43]. None of the studies included relevant data to explore the relationship between symptoms and the secondary attack rate.

There are several limitations to our review. We aimed to include all studies with relevant evidence; this resulted in the inclusion of studies with substantial heterogeneity, much of which was due to a lack of uniformity across jurisdictions and time. Notably, there was wide variation in case definitions, although most emphasized traditional manifestations of clinical disease [9, 10, 44]. Differences in symptom ascertainment, comprehensiveness of testing, and the types of vaccines used limited our ability to pool data or conduct subgroup analyses. Consequently, we present ranges, which demonstrate the ubiquity of nontypical infection but do not provide specific estimates of the magnitude. While stricter inclusion criteria could have reduced this variation, it also would have severely limited the evidence included.

Another limitation is that multiple laboratory methods and a range of assay cutoffs were used to confirm pertussis infection. In addition to the inherent limitations of each test, a large proportion of asymptomatic infection was based on serological evidence, which is not standardized and from which it is difficult to distinguish current infection from a recent but prior infection or recent vaccination. Additionally, the timing of sample collection, which may heavily influence the laboratory test result, was rarely reported. Antibiotic chemoprophylaxis in household contacts may also influence laboratory test results as well as disease severity, but we were unable to explore these effects due to limited reporting across studies. Similarly, in cross-sectional studies there is potential for case misclassification dependent on the contact's stage of disease at the time of investigation, although we expect this to have a minimal effect on our findings as these studies identified relatively small proportions of asymptomatic disease.

There is a lack of clarity regarding whether a positive laboratory test in an asymptomatic individual is indicative of infection, colonization, or immune boosting. Current evidence fails to resolve this ambiguity, and there is a need for continued research using both human and animal studies to explore the significance and role of asymptomatic infection in pertussis transmission and resurgence [41, 45].

Asymptomatic pertussis infection has often been considered infrequent and to pose little risk to others as there is no clear mechanism for asymptomatic transmission [31, 39]. Our review demonstrates that the prevalence of asymptomatic infection is high and that the frequent close contact that occurs in household settings may provide sufficient opportunity for *B. pertussis* to spread, even if transmission from asymptomatic cases is uncommon through general population mixing [24, 41].

Future studies should be designed to generate direct evidence of the prevalence of mild/atypical and asymptomatic pertussis infection and the ability of asymptomatic cases to transmit disease. These may include household studies with a primary objective of characterizing asymptomatic infection and transmission [46] or even carefully designed and ethically conducted human challenge studies, particularly those that include vaccinated individuals [47, 48].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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