ORIGINAL ARTICLE

Severe and unrecognised: pertussis in UK infants

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Aims: To diagnose pertussis using culture, polymerase chain reaction, and serology, in children admitted to intensive care units (PICUs) and some paediatric wards in London, and in their household contacts to determine the source of infection.

Methods: Infants <5 months old admitted to London PICUs between 1998 and 2000 with respiratory failure, apnoea and/or bradycardia, or acute life threatening episodes (ALTE), and children <15 years admitted to paediatric wards at St Mary's and St George's Hospitals between 1999 and 2000 with lower respiratory tract infection, apnoea, or ALTE were studied.

Results: Sixty seven per cent of eligible children (142/212) were recruited; 23% (33/142) had pertussis, 19.8% (25/126) on the PICU and 50% (8/16) on wards. Two died. Only 4% (6/142) were culture positive. Pertussis was clinically suspected on admission in 28% of infants (7/25) on the PICU and 75% (6/8) on the wards. Infants on PICU with pertussis coughed for longer, had apnoeas and whooped more often, and a higher lymphocyte count than infants without pertussis. Pertussis and respiratory syncytial virus (RSV) co-infection was frequent (11/33, 33%). Pertussis was confirmed in 22/33 (67%) of those who were first to become ill in the family. For 14/33 children the source of infection was a parent; for 9/33 the source of pertussis was an older fully vaccinated child in the household.

Conclusions: Severe pertussis is under diagnosed. An RSV diagnosis does not exclude pertussis. Future changes to the UK vaccination programme should aim to reduce pertussis transmission to young infants by their parents and older siblings.

Case reports, statutory notifications, and laboratory reports indicate that young infants are continuing to develop pertussis in the UK despite good vaccination coverage, with pertussis vaccine given at 2, 3, and 4 months of age.[1 2] Such traditional methods of ascertainment are known to underestimate the level of disease.[3] Doctors fail to notify even cases of clinically typical pertussis admitted to hospital. General practitioners are often reluctant to carry out appropriate investigations, such as pernasal swabs. Even if appropriate specimens are taken, culture has sensitivity as low as 20–40%,[4 5] because the organism is delicate and the likelihood of culturing it falls if there is any delay in processing specimens. Culture is also more likely to be unsuccessful the longer the time since the onset of illness. Diagnostic sensitivity can be maximised by supplementing culture with polymerase chain reaction (PCR) methods and serology. PCR is more sensitive than culture as it does not require organisms to be viable. Serology is particularly useful in diagnosing infection in patients who have been coughing for some weeks, when both culture and PCR would be anticipated to be unhelpful. Serology has undergone extensive evaluation and standardisation in recent years (ESEN). We applied PCR and serological diagnostic methods to find out the level of pertussis in hospitalised children and their household contacts. We aimed to determine whether parents or siblings infect infants too young to be directly protected by vaccination, in order to inform UK pertussis vaccination policy.

METHODS

The main study was carried out in paediatric intensive care units (PICU) for two years from November 1998, with a recruitment break for the respiratory syncytial virus (RSV) season (November to February) of the 1999/2000 winter. A smaller study was carried out on paediatric wards starting in July 1999. Eligible infants for the PICU study were under 5 months of age and admitted between November 1998 and October 1999 or March and October 2000 with any of the following:

- Respiratory failure (defined as respiratory insufficiency requiring admission to PICU but excluding persistent pulmonary hypertension of the newborn, meconium aspiration, hyaline membrane disease, and respiratory failure due to known structural airway problem)
- Apnoea and/or bradycardia
- Acute life threatening episode (ALTE).

Eligible children for the ward study were under 15 years and admitted between July 1999 and October 1999 or March and October 2000, with lower respiratory tract infection (excluding asthma and croup), apnoea, or ALTE. All household contacts were included.

The study was carried out with research ethics committee approval from all participating centres and with written informed consent of participants. Research nurses collected information onto a standard questionnaire about the clinical features of illness in cases and contacts and the results of any hospital investigations from parents, clinical notes, and pathology systems. This included all hospital results of standard investigations including pertussis culture. Vaccination status of infants, children, and parents was based on parental reporting. The recommended number of doses of pertussis vaccine for the age of infants given in the national vaccination schedule was compared with the number of doses actually received.

Abbreviations: ALTE, acute life threatening episode; ESEN, European Sero-epidemiology Network; PCR, polymerase chain reaction; PICU, paaediatric intensive care unit; PT, pertussis toxin; ptxA, pertussis toxin gene; RSV, respiratory syncytial virus

Table 1 Laboratory results for children with microbiologically confirmed pertussis (excludes nine epidemiologically linked cases)

	Culture positive		Culture negative			
PCR	Serology positive	Serology not received	Serology positive	Serology negative	Serology not received	Total
PICU						
Positive	2	0	3	4	4	13
Negative	0	0	2	*	*	2
Not received	1	0	1	*	*	2
Ward						
Positive	1	1	2	0	1	5
Negative	0	0	1	*	*	1
Not received	1	0	0	*	*	1
Total	5	1	9	4	5	24

*Specimen results would not meet the diagnostic criteria for a case of pertussis and so would not appear in this table.

Research nurses obtained nasopharyngeal aspirate, and acute and convalescent sera from eligible infants on PICU. From the generally older eligible children on the wards, they took pernasal swabs. Pernasal swabs were taken from adult and child household contacts and a single blood specimen from adult contacts only. For mothers only, we obtained stored antenatal serum where available.

A case of pertussis infection was diagnosed if one or more of the following was found:

- *Bordetella pertussis* isolated by culture
- Polymerase chain reaction (PCR) positive for two targets—the pertussis toxin gene (ptxA) and insertion element IS481 sequences
- PCR positive with one target in duplicate samples
- Pertussis toxin (PT) IgG antibody levels greater than 100 U/ml.

If a child did not meet these criteria but one or more of their household contacts had been ill and met the diagnostic criteria for confirmed pertussis, the child was designated an epidemiologically linked case. Infants with pertussis were compared in the analysis with other recruited infants who did not meet the study diagnostic criteria for pertussis.

Household members were regarded as having a confirmed infection with *B pertussis* if they met the criteria above for a case or, in the absence of a clinical specimen, they had an illness compatible with pertussis and were epidemiologically linked to another confirmed case in the family.

The source of infection was defined by the individual in the household with the earliest date of onset of cough (or of admission for two infants with no cough). If household members became ill with dates of onset separated by five days or less, they were considered to be co-primary cases.

For the first year, samples were transported to the laboratory within four hours of collection and processed within one hour of delivery. Culture of these samples was carried out by standard PHLS methods.[6] In the subsequent year, samples were frozen rapidly to −70°C and transported frozen. Pertussis PCR was carried out using single round PCRs to minimise contamination risk, with two independent targets providing mutual confirmation and a range of controls. The ptxA PCR targets the pertussis toxin promoter region yielding a 191bp product and has a reported sensitivity of six bacteria per reaction.[7] The IS481 PCR targets the *B pertussis* insertion sequence IS481, yielding a 146bp product, and has a reported sensitivity of three bacteria per reaction.[8] Control measures included: for sensitivity, titration of a positive control within each run; for specificity, a dummy sample (phosphate buffered saline in place of the clinical sample) per run, and 2–3 water blanks per run. Serology for pertussis toxin (PT) IgG antibody using PT antibody as a marker of recent infection with pertussis was undertaken as previously described.[9] Use of paired and single high titre diagnostic criteria have been evaluated in the European Sero-epidemiology Network (ESEN) project and elsewhere.[10] RSV and influenza detection were carried out by multiplex nested PCR.[11] RSV positive results from nasopharyngeal aspirate which had been taken more than 48 hours after admission were excluded as potentially nosocomial infections. Clinicians were aware that the study was ongoing but laboratory results were not made available in real time.

For the data analysis, groups were compared for categorical variables using χ^2 tests, and for continuous variables by *t* test or by Mann-Whitney test for non-parametric data.

RESULTS

We recruited 126/183 eligible infants (69%) admitted to the PICUs and 16/29 children (55%) admitted to wards. Nurses obtained 79% specimens within two days of admission, with a median time of one day between admission and sampling. The mean duration of illness prior to taking specimens was 13 days for the ward cases and 18 days for PICU cases ($p = 0.4$). For the household contacts, questionnaire data were available for 282/300 adults (94%) and 186/192 other children in the household (97%). Specimens were obtained from 81% adult and 43% child contacts.

Pertussis PCR was positive in 18/138 (13%) specimens received from recruited children, 16/235 (7%) pernasal swabs from their adult contacts, and 4/85 (5%) pernasal swabs from child contacts. Pertussis was diagnosed according to the case definition in 25/126 (19.8%, 95% confidence interval (CI) 12.9% to 26.8%) infants on PICU and 8/16 (50%, 95% CI 24.7% to 75.3%) children on the wards. Of the 25 cases on the PICU, 17 were laboratory confirmed and eight were epidemiologically linked cases (table 1). Five infants with confirmed pertussis on PICU were diagnosed by pertussis PCR alone, and two were diagnosed on the basis of serology only (table 1). Specimens from 2/126 (2%) PICU infants and one ward infant were culture positive. Of the ward cases, 7/8 were confirmed and one was epidemiologically linked. Of the total of nine epidemiologically linked infants on the PICU and wards, three had equivocal PCR results and negative serology, and six were negative by PCR but no serum was obtained. Pertussis was suspected on admission in 7/25 (28%) infants who met the study criteria on the PICU and 6/8 (75%) infants on the wards. There was a tendency for the ward cases to have more "typical" features (table 2).

Antibiotics had been given prior to admission to seven children with pertussis and 15 with another diagnosis. This had included a macrolide antibiotic in one child with confirmed pertussis and three with other diagnoses. A further five children had specimens taken for the study after starting

Table 2 Clinical features of children on PICU and wards with pertussis (including linked cases) compared with children on PICU with other diagnoses (categorical variables)

	Ward: pertussis (n=8)	PICU: pertussis (n=25)	PICU: other diagnoses (n=101)
Cough	8/8	23/25	82/101
Paroxysmal	6/8	14/24	34/89
Whoop	4/4	9/24	3/87
Vomiting	4/4	15/25	49/101
Fever	5/8	11/25	45/101
Apnoea	3/8	17/25	40/100
Cyanosis	8/8	16/25	51/100
Pneumonia	0	5/25	14/96
Conjunctival haemorrhage	0	1/25	3/101
Death	0	2/25	6/101

in-patient antibiotics. Pertussis was confirmed in none of these children. Four of these five infants received a macrolide antibiotic for one to seven days before the specimens were obtained. All infants with pertussis received antibiotics during the PICU admission, but for 7/25 this did not include a macrolide antibiotic.

Infants admitted to the PICU with pertussis were not more likely to cough than infants with other diagnoses (table 2). However, they were significantly more likely to have had apnoeas ($p = 0.03$), and to whoop ($p < 0.005$). Of infants with an admission diagnosis of apnoea alone, 3/10 (33%) had pertussis. Two infants died, both previously well infants born at full term, compared with six deaths of infants without pertussis. The duration of ventilation, stay on the PICU, and total hospital admission of the 25 infants with pertussis were not significantly different to those with other diagnoses, but they had longer durations of cough and higher lymphocyte counts (table 3). The ward children had a median duration of cough of 12 days (interquartile range (IQR) 7 to 19.3), median lymphocyte count of 15.6×10^9/l (IQR 2.3 to 7.8), and median length of stay of 7.0 days (IQR 10.5 to 23.5). Similarly to the PICU infants, the ward children with pertussis had a longer median duration of cough ($p = 0.03$), and higher lymphocyte count ($p = 0.004$) than children with other diagnoses, but their overall length of admission was not significantly different ($p = 0.9$).

Most PICU infants with pertussis were unvaccinated because they were too young; 16/25 were less than 2 months old. PICU infants with pertussis were as likely to have received fewer than the recommended number of doses of pertussis vaccine than those without pertussis (5/25 (20%) compared with 33/101 (32.7%); $p = 0.2$). Ward babies were "under vaccinated", with 5/8 (71.4%) with pertussis having received fewer doses than recommended for their age versus 1/8 (12.5%) without pertussis ($p = 0.1$).

In total, 26/289 contacts of recruited PICU infants and 6/39 children recruited on the wards had laboratory confirmed pertussis. The families of a baby with pertussis had a median number of laboratory confirmed cases (in addition to the hospitalised child) of one, with a range of 0–2 cases. Sixty of 111 (54%) contacts of children with confirmed pertussis had a cough versus 144/351 (41%) contacts of children admitted with other diagnoses ($p = 0.02$). Duration of cough was available for 168/204 coughing contacts. The median duration of cough in contacts of pertussis cases was 13.5 days compared with 7.5 days in other contacts ($p = 0.04$). A clinical case definition of 21 or more days coughing plus at least one of paroxysms, whooping, or vomiting was met by 10/111 (9%) contacts of pertussis cases compared with 9/351 (3%) other contacts ($p = 0.006$). Pertussis was confirmed in 6/17 (35%) contacts who met this case definition compared with 26/311 (8%) who did not ($p = 0.003$).

Primary cases (the source of infection) included parents and other children in the households (table 4); 67% of primary cases were laboratory confirmed. The greatest level of non-confirmation occurred when a child was the primary case, largely because we obtained fewer specimens from children. Of seven unconfirmed primary cases in child contacts, no specimens were obtained for four. Two of the three unconfirmed cases with a negative pertussis PCR result met a clinical case definition of coughing for 21 days or more, and coughed for 30 and 60 days respectively. Seven PCR positive contacts and a three contacts with serological evidence of recent infection were asymptomatic prior to and at the time of sampling and did not develop symptoms in the 6–8 weeks before follow up of the infant.

All siblings who were a possible source of infection were reported to be fully vaccinated. In total, 91% of adult contacts (30/33) and 97% of child contacts (29/30) of PICU infants with microbiologically confirmed pertussis reported having been vaccinated for pertussis in the past. This was not significantly lower than reported for contacts of PICU infants without pertussis (adults: 94%, 133/141; children: 95%, 120/127).

RSV co-infection occurred in nine PICU infants with pertussis and two ward children. Infants on PICU with

Table 3 Clinical features of children on PICU with pertussis (including linked cases) compared with children on PICU with other diagnoses; continuous variables

	PICU: pertussis (n=25)		PICU: other diagnoses (n=101)		Mann-Whitney test
	Mean	Median	Mean	Median	
Duration of cough (days)	15.2	8.5	11.0	4.0	0.003
Lymphocyte count (× 10^9/l)	8.8	7.8	4.5	3.5	0.003
Duration of ventilation (days)	4.6	3.5	4.8	3.0	0.4
Length of stay on PICU (days)	5.7	4.5	8.2	4.0	0.8
Length of total hospital admission (days)	15.6	13.0	15.2	10.0	0.2

Table 4 Proportion of laboratory confirmed cases among primary (first) cases in families of pertussis cases in PICU and wards

Relationship	PICU	Ward	Total
Parent	10/11	2/3	12/14
Sibling	0/6	2/3	2/9
Baby or co-primary	6/8	2/2	8/10
Total	16/25	6/8	22/33

co-infection did not have more severe illness than those with other diagnoses, with no statistically significant difference in duration of ventilation, admission to PICU, or total hospital admission.

DISCUSSION

Pertussis is a more frequent cause of admission to PICU than generally recognised. Although the numbers in this study are small, for most of the infants the presentation was not typical, the diagnosis was unsuspected, and the case would not have been investigated or notified as pertussis. The combination of pertussis PCR and serology greatly enhanced diagnostic sensitivity in young hospitalised infants, with implications for surveillance and infection control. Hospitalised infants with pertussis including fatal cases are under notified.[3 12] This study shows that, in addition to under notification, under ascertainment is occurring of severely affected infants requiring admission to a PICU. The true number of severe infections, particularly fatal cases, is extremely important in determining the likely benefits of booster vaccinations in modelling different policy options.[13] On the basis of this study, the Health Protection Agency now offers PCR and serology to improve diagnosis of pertussis for such infants, and the results are contributing to enhanced surveillance.[1]

Twenty eight per cent of infants with proven pertussis did not receive a macrolide antibiotic and risked transmitting the infection to staff and other patients. Pertussis is extremely infectious, and a missed diagnosis in PICU may lead to outbreaks among extremely vulnerable infants.

Infants with pertussis were not more ill than those with other diagnoses causing similar clinical syndromes. Co-infection with RSV occurred frequently but did not adversely affect outcome. Samples were collected too close to the point of admission for these co-infections to be nosocomial. Co-infection with pertussis and RSV has been described previously to cause severe infections.[14 15] The different findings in this study may be a chance result because the number of co-infections was small. Alternatively it may reflect greater sensitivity of diagnostic methods for both pertussis and RSV, which means that either or both may be detected outside the window of acute infection. In addition, either agent may influence the transmissibility of the other without influencing disease severity. It is important to recognise co-infections, both for infection control and clinical management. A diagnosis of RSV does not exclude pertussis, and vice versa.

Ten contacts had no symptoms, but *B pertussis* DNA was detected by PCR of nasopharyngeal swab, or PT IgG levels indicated recent infection. There are several possible explanations, including false positive results, "carriage" of *B pertussis*, modification of disease through vaccination, subclinical infection with immunological boosting, and incubating disease. While false positive results are always a risk of PCR, we applied stringent methods and we believe that the diagnostic criteria erred on the side of risking false negative results rather than false positive ones. Although *B pertussis* carriage has not been recognised previously,[16] we may need to change our perspective in the light of the results of highly sensitive diagnostic methods. If carriage does occur, this might explain persistence of the infection in the community despite sustained high vaccination coverage.

Although the primary (source) cases were defined only by date of onset of cough, most were also laboratory confirmed. The role of possible asymptomatic infections in spreading pertussis is unknown, but symptomatic ones are likely to be more important for transmitting the infection through droplets. Parents appear to be the most important source of infection, but siblings also appear to bring pertussis into families. Laboratory confirmation was less frequent in siblings than parents. This was partly because specimens were not obtained. In addition, as all siblings were vaccinated, they may have presented with milder disease that is less likely to be detected by PCR. For the cases where the source of the infection was not identified, the source may include visitors to or contacts outside the household. Nearly all household contacts reported having been vaccinated in the past, and yet infants were still infected, as has also been observed in France.[17]

The study was carried out during the inter-epidemic years of 1998–2000, in which notifications were at the lowest levels on record in the UK. Consequently, the findings represent a minimum estimate of the burden of disease. PCR and serology add considerably to sensitivity of pertussis diagnosis in PICU. These diagnostic methods should be used routinely, at least in this setting. There is considerable under recognised morbidity and mortality from pertussis in infants presenting to PICUs in London, despite high vaccination coverage in their household contacts. The finding that pertussis continues to affect young infants and the degree of its under ascertainment, as well as the source of infections in families, helped to inform the decision to introduce a preschool pertussis booster into the UK vaccination schedule from November 2001.[13] Any future changes to the immunisation programme may need to take into account the fact that in the UK, adults may be transmitting whooping cough to infants.

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Contribution of authors: NS Crowcroft took a lead in design, writing the protocol, securing ethics committee approval, coordinating the study, supervising the research nurses, assisting with recruitment and follow up, carrying out the epidemiological analysis, and writing the paper. R Booy had the idea to do a study, helped with study design implementation, and supervision of research nurses, and contributed to analysis and writing the paper. T Harrison helped with design of the study, was responsible for the bacteriological investigations, and contributed to analysis and writing the paper. L Spicer was the lead research nurse, secured ethics committee approval for the study extension, coordinated the second half of the study, and contributed to data entry, analysis, and writing the paper. J Britto helped with design and implementation of the study, and contributed to analysis. Q Mok helped with implementing the study, and contributed to analysis and writing up. P Heath helped with implementing the study, and contributed to writing up. I Murdoch helped with implementing the study, and contributed ideas and to analysis. M Zambon provided virology investigation, and helped with interpretation of RSV results and writing up. R George helped with design and implementation of the study, and contributed to analysis and writing up. E Miller contributed to protocol writing, analysis, and writing the paper.

Other contributors not listed as authors: Ting Li and Oceanis Tzivra carried out the pertussis laboratory work; Angela French carried out the RSV and influenza PCRs.

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