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Bordetella pertussis surveillance in England and Wales: 1995–7

P. G. VAN BUYNDER[1], D. OWEN[2], J. E. VURDIEN[1], N. J. ANDREWS[1], R. C. MATTHEWS[2] AND E. MILLER[1]*

[1] *Communicable Diseases Surveillance Centre, 61 Colindale Ave, Colindale, NW9 5EQ UK*
[2] *Pertussis Reference Laboratory, 2nd Floor, Clinical Sciences Building, Central Manchester Healthcare NHS Trust, Manchester Royal Infirmary, Manchester, M13 9WL UK*

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SUMMARY

Available data sources on disease due to *Bordetella pertussis*, including notifications, hospital admissions, deaths, and an enhanced laboratory-based surveillance system commenced in January 1994, were reviewed for the period 1995–7. Pertussis notifications continued their approximately 3-year cycle although at historically reduced levels. A slight seasonal increase in late summer/early autumn existed over and above a relatively constant background rate. Over time, the proportion of pertussis cases in younger, unvaccinated children, and to a lesser extent, adolescents and young adults, is increasing. There is a continuing significant and under-reported mortality associated with pertussis in the very young age group. Disease due to serotype 1,2 is on the increase despite persistent high vaccination levels and this serotype causes more severe disease. The provision of preventative antibiotics prior to disease onset reduced the severity of the disease but its use remains uncommon in England and Wales. While overall levels of pertussis notifications have declined in recent times, vaccination efficacy wanes with increasing age, and pertussis remains a significant cause of mortality and severe morbidity in the very young. This could be reduced by timely booster vaccination and increased recognition of mild disease in older cases followed by early antibiotic therapy for the very young household contacts.

INTRODUCTION

A number of recent international reports have focused on a resurgence of whooping cough notifications despite high vaccination rates, often associated with significant mortality in very young children [1–3]. In part, these increases have been attributed to the growth of a susceptible adult population [4]. In England and Wales the number of cases of whooping cough notified, after allowing for epidemic cycles, has reached historically low levels since the attainment of consistently high coverage rates for the primary vaccination course over the last decade [5]. While notifications are down, concern has been expressed about the possibility of increasing disease in very young children and a possible lower duration of efficacy associated with the accelerated vaccination schedule used [6].

In order to monitor whooping cough in England and Wales and vaccine efficacy, and to assess the need for pertussis booster vaccination, an enhanced surveillance system was commenced in 1994 [7]. We reviewed the information available from this system for the years 1995–7, as well as information available from other sources, in order to assess vaccine efficacy, trends in disease transmission, variation in circulating serotypes and the benefits of prophylactic erythromycin chemotherapy.

* Author for correspondence.

MATERIALS AND METHODS

Data sources

Notifications of clinically diagnosed cases of whooping cough and number of deaths were obtained from the Office of National Statistics (ONS) for the years 1991–7. Non-aggregated hospital admission data, for England only, was obtained from computerized Department of Health hospital episodes statistics (HES). HES data were only available up to the 1995/6 financial year. Information on cases of bacteriologically confirmed infections with *Bordetella pertussis* was obtained from the PHLS Communicable Disease Surveillance Centre (CDSC) which receives reports on culture positive pertussis from laboratories in England and Wales. The Pertussis Reference Laboratory (PRL) in Manchester also provides reports on isolates sent for serotyping. Extra information on vaccination history, severity, antibiotic prophylaxis and treatment, and history of exposure is sought for all these cases (enhanced surveillance). The PRL provided the results of serotyping of isolates of *B. pertussis*. Vaccine coverage estimates were derived from annual returns by district health authorities to the Department of Health and from quarterly reports of the COVER (Cover of vaccination evaluated rapidly) programme for children under 2 years old [8, 9].

Data analysis

Data were analysed using the SPSS [10] and GLIM statistical packages [11]. Confidence intervals for vaccine efficacy were calculated by fitting a logistic regression model to the proportion of cases fully vaccinated (after excluding those partially vaccinated) with an adjustment for vaccine coverage [12]. This model also enabled estimation of linear trends over the 3 years where the trend parameter (t) is defined as the annual proportional drop in vaccine efficacy from 100%. This is equivalent to the proportional increase in the relative risk of disease in vaccinated compared to unvaccinated. An estimate of the linear trend for the decline in vaccine efficacy with increasing age was also calculated.

RESULTS

Notifications

Pertussis notifications increased in each of the study years after 1869 cases (the lowest annual number since notifications began) was notified in 1995. This is shown in Table 1. Despite the increase, the number of notifications remained below those seen in 1993/4 [5] and well below the notification rates prior to increased vaccine coverage. The change from year to year and the peaks during epidemic periods have become less marked of recent times and notifications in the 1990s are occurring in different age groups within the population. The proportion of notifications occurring in patients over 15 years of age since 1991, has increased from 4·4 to 9·3% and there has been a marked increase in the proportion occurring in children under 6 months of age from 6·3% of notifications in 1991 to 19·1% of notifications in 1997. This is shown in Figure 1. In addition to increasing proportions, the absolute number of notifications in these two age groups was higher in 1997 than in any other year since 1990 (Table 1).

HES data

There were a total of 647 admissions to hospitals in England with a diagnosis of whooping cough in 1995, (ICD-10 code A27 in either primary or other diagnosis fields) with 65% occurring in infants less than 1 year of age. The age specific admission rate for whooping cough decreased with increasing age and in children less than 6 months of age, was higher than the officially notified rate of illness. These figures are shown in Table 2 and suggest that both laboratory reports and notification data substantially underestimate the true burden of pertussis-attributable morbidity in young infants.

Enhanced surveillance system

The enhanced surveillance system identified 1368 pertussis isolations over the 3-year period 1995–7, of which 250 were detected solely by the reconciliation of CDSC and PRL reports. Isolations occurred all year but peaked in the late summer/early Autumn months of August and September and were lowest in mid-Winter. A similar seasonal pattern was seen in the review of hospital admission statistics in 1995. There was an even gender distribution (males 49·8%). Enhanced surveillance selectively picked up younger more severe cases than those identified through ONS notifications. During the 3 years studied 729 cases (53%) were less than 6 months' of age, compared to 16% of notified cases.

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Table 1. *Pertussis notifications by age group, 1990–7*

Age group	Year							
	1990	1991	1992	1993	1994	1995	1996	1997
< 6 mths	939	325	214	363	385	252	359	570
6–11 mths	653	292	133	174	164	83	93	132
1–4 years	6167	2158	878	1486	1413	670	724	919
5–14 years	6667	2134	915	1798	1679	686	974	1053
> 14 years	672	231	133	225	247	147	201	277
Total*	15286	5201	2309	4091	3964	1869	2387	2989

* Includes cases where age unknown.

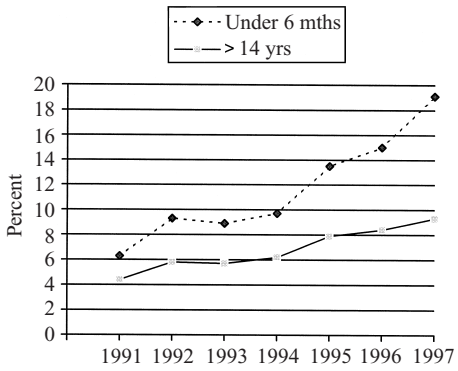

Fig. 1. Pertussis notifications 1991–7. Trend in age cohort proportions.

Mortality

A total of 12 deaths were identified from the enhanced surveillance system during the 3 years. Nine of these were male and 10 were less than 2 months of age. Of the 2 children aged 6 months, 1 was known to have received no vaccinations and the vaccination status of the other was unknown. Mortality data from ONS identified only 5 pertussis deaths during the same period. Of these 2 had been identified in the enhanced surveillance database and all 5 cases were less than 3 months of age.

A review of hospital inpatient data for the 15 month period available identified 4 deaths due to pertussis. By matching on date of birth, date of death, sex and district, 2 of the 4 HES deaths had been identified in the enhanced surveillance database; and 1 of the 2 also appeared in the ONS statistics. Three were less than 2 months of age and 1 child with multiple congenital abnormalities was aged 9 years.

Anecdotal information (R. Booy, personal communication) identified a pertussis related death in another child of less than 2 months not recorded in any of the above systems; thus, there were at least 18 pertussis related deaths in the 1995–7 period and this is likely to be an underestimate of the true number.

Using capture–recapture methods, which use patterns of replication in varying data sources to estimate proportions identified by none of the sources, a likelihood profile to correct for the varying ascertainment was fitted [13]. This modelling produced an estimate of 10 for the number of deaths not detected with a 95% confidence interval range of 1–40. We estimate the total number of pertussis deaths during the 3 years to be 28 (95% CI 19–58).

Severity of illness

Information was available from the enhanced database on hospital admission and the occurrence and nature of any complications. Of the 1177 cases where the information was recorded, 787 (67%) were admitted to hospital. Multivariable analysis with the likelihood of hospital admission as the dependent variable demonstrated a protective effect of vaccination independent of age group, serotype and the use of preventative therapy. Unvaccinated patients were 1·5 times more likely to be admitted to hospital than vaccinated children. The results of the GLIM model are shown in Table 3. There were no regional or gender differences associated with admission to hospital.

Pertussis in vaccinated cases produced a milder illness as judged by complications reported on the enhanced surveillance form. In addition to the reduced risk of hospital admission (Table 3) patients who had received any pertussis vaccination doses were less likely to have complications, namely apnoea attacks, convulsions and pneumonia. We divided those with any vaccination into groups receiving 1 dose, 2 doses, or more than 2 doses of vaccine in a multivariable analysis of the likelihood of complications which included age as a confounder. The odds ratios compared to no vaccination were 0·50, 0·39 and 0·64

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Table 2. *Comparisons of age-specific pertussis rates by identification method, England 1995*

	Hospital admissions		Notifications		Isolates	
Age group	Number	Rate*	Number	Rate	Number	Rate
< 3 mths	252	164·0	139	90·5	48	31·2
3–5 mths	117	76·1	99	64·4	58	37·7
6–11 mths	52	16·9	78	25·5	9	2·9
1–4 years	142	5·5	628	24·3	41	1·6
5+years	84	0·2	813	1·8	44	0·1
Total	647	1·3	1757	3·6	200	0·4

* Rate per 100000.

Table 3. *Factors influencing likelihood of admission*

Multivariable analysis results for odds of admission to hospital			
Factor*	Level	Odds ratio (95% CI)	*P*-value
Age group	< 2 months	1·0 (baseline)	< 0·0001
	2–5 months	0·46 (0·25 to 0·86)	
	6–11 months	0·19 (0·08 to 0·45)	
	1–4 years	0·07 (0·04 to 0·13)	
	5–14 years	0·03 (0·02 to 0·06)	
Year	1995	1·0 (baseline)	0·45
	1996	1·19 (0·71 to 1·99)	
	1997	1·18 (0·73 to 1·96)	
Serotype of isolate†	1,2	1·0 (baseline)	< 0·0001
	1,3	0·46 (0·30 to 0·70)	
	1,2,3	0·17 (0·04 to 0·80)	
	Unknown	0·70 (0·47 to 1·05)	
Vaccination status (any doses)	Yes	1·0 (baseline)	0·018
	No	1·51 (1·07 to 2·14)	
Received preventative therapy	Yes	1·0 (baseline)	0·022
	No	1·95 (1·10 to 3·44)	
Sex	Male	1·0 (baseline)	0·86
	Female	1·03 (0·75 to 1·42)	

* Lists all levels of all factors included.
† Cases without a serotype included as an unknown group to increase data in model.

respectively. These odds ratios are not statistically significantly different from one another ($P = 0{\cdot}67$) so within the vaccinated group the odds ratios can be summarized by combining them as one group as in Table 4. Unvaccinated children are 1·82 times as likely as vaccinated children to exhibit complications.

Preventative therapy

Information on the provision of a preventative course of erythromycin therapy and its duration was available for 1108 (81%) patients. Of these, only 86 (7·8%) received preventative therapy, the lowest proportion (5·3%) being in the 0–2 month age group and the highest proportion (14·9%) in the 6–11 month age group. The difference between age groups was not statistically significant ($\chi^2 = 7{\cdot}4$, D.F. = 4, $P = 0{\cdot}12$). People admitted to hospital were less likely to have received preventative therapy than those with less severe illness (44\660 c.f. 40\318, $\chi^2 = 8{\cdot}4$, $P = 0{\cdot}04$). Children known to have been vaccinated were no less likely to have been offered preventative therapy than unvaccinated children ($\chi^2 = 0{\cdot}5$, $P = 0{\cdot}8$). There was no increase in the provision of preventative therapy over the course of the 3 years studied ($\chi^2 = 0{\cdot}04$, $P = 0{\cdot}998$). In multivariable logistic regression models,

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Table 4. *Factors affecting disease severity*

Multivariable analysis results for odds of any complication*			
Factor	Level	Odds ratio (95% CI)	*P*-value
Age group	< 2 mths	1·0 (baseline)	< 0·0001
	2–5 mths	0·60 (0·40 to 0·91)	
	6–11 mths	0·27 (0·12 to 0·59)	
	1–4 years	0·23 (0·13 to 0·39)	
	5–14 years	0·14 (0·08 to 0·24)	
Year	1995	1·0 (baseline)	0·62
	1996	0·81 (0·51 to 1·28)	
	1997	0·80 (0·52 to 1·23)	
Vaccinated	None	1·0 (baseline)	0·0013
	One or more	0·55 (0·38 to 0·79)	
Sex	Male	1·0 (baseline)	0·43
	Female	1·12 (0·84 to 1·50)	

* 1114 observations included.

Table 5. *Serotype of* B. pertussis *isolates: trends over time and associated factors*

		Serotype			
Year	Parameter	Serotype 1,2	Serotype 1,3	Serotype 1,2,3	Significance
All years	Admitted	235	223	7	
	Not admitted	80	144	9	$\chi^2 = 18{\cdot}5$, $P < 10^{-3}$*
All years	Complications	96	78	3	
	No complications	222	298	12	$\chi^2 = 8{\cdot}4$, $P = 0{\cdot}02$*
1995	Total isolates	36	64	3	
1996	Total isolates	92	112	8	
1997	Total isolates	224	235	6	$\chi^2 = 10{\cdot}0$, $P = 0{\cdot}04$*
All years	Vaccinated†	139 (71)	141 (74)	5 (4)	
	Not vaccinated	188	226	10	$\chi^2 = 1{\cdot}5$, $P = 0{\cdot}47$
All years	Age < 2 months	86	108	6	
	Age 3–5 mths	118	112	3	
	Age 6–11 mths	17	16	0	
	Age 1–4 years	70	82	4	
	Age 5–14 years	60	89	4	$\chi^2 = 7{\cdot}6$, $P = 0{\cdot}47$

* Pearson two-sided χ^2.
† Numbers are those receiving any vaccination with fully vaccinated numbers in parentheses – neither model shows a significant difference between serological types.

those patients who have not received preventative therapy were 1·9 times more likely to be admitted to hospital than those receiving erythromycin ($P = 0{\cdot}02$). This association was independent of the confounders, age of patient and vaccination status (Table 3).

Bordetella pertussis serotypes

Serotyping results were available for 780 of the 1368 laboratory confirmed cases over the 3-year period. Most serotypes were type 1,3 (52·7%) with only 17 (1·2%) being serotype 1,2,3. However, the proportion due to serotype 1,3 decreased steadily over the 3 years studied, with a concomitant increase in the proportions of serotype 1,2 infections and this trend over time was significant (Overall $\chi^2 = 10{\cdot}0$, D.F. = 4, $P = 0{\cdot}04$, χ^2 for trend = 3·9, D.F. = 1, $P = 0{\cdot}048$) (Table 5). In addition, during the study period and for each of the individual years, serotype 1,2 caused more severe illness as evidenced by rates of admission to hospital and by the documented notation of complications on the enhanced surveillance data form. This increased severity of serotype 1,2 was not related to differences in proportions fully vaccinated, partially vaccinated

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Table 6. *Vaccine efficacy according to age, using screening method*

Age group	Year	Vaccination status			National vaccine coverage	Vaccine efficacy (95% confidence intervals)	Trend estimate
		Fully vaccinated	Partially vaccinated	Unvaccinated			
6–11 mths	1995	3	0	6	87	92·5 (70·1–98·1)	
1–4 years		16	1	33	92	95·8 (92·3–97·7)	
5–14 years		5	1	40	70	94·6 (86·4–97·9)	
6–11 mths	1996	2	1	15	87	98·0 (91·3–99·5)	
1–4 years		41	4	42	93	92·7 (88·7–95·2)	
5–14 years		40	8	49	73	69·8 (54·2–80·1)	
6–11 mths	1997	7	1	23	87	95·5 (89·4–98·1)	0·91 (0·38–2·20)*
1–4 years		80	5	54	93	88·9 (84·3–92·1)	1·60 (1·15–2·24)*
5–14 years		59	8	77	76	75·8 (66·0–82·8)	1·51 (0·49–4·81)*
6–11 mths	All years 95–97	12	2	44	87	95·8 (89·4–98·1)	
1–4 years		137	10	129	93	91·8 (86·6–95·0)	
5–14 years		104	17	166	73	75·8 (63·8–86·8)	2·44 (1·85–14·89)†

* Trend estimate over time.
† Trend estimate with increasing age.

or to differences in the age distribution of cases with differing serotypes. In multivariate analysis with the likelihood of admission as the dependent variable, and including both age group and vaccination status as part of the model, serotype 1,2 was twice as likely as serotype 1,3 to be associated with an admission to hospital and seven times as likely as serotype 1,2,3 to be admitted (Table 5).

Source of infection

In 282 enhanced surveillance patients a likely source of infection was recorded (20·6%). Of these, 204 were sources within the home, 43 within a school, 14 within a playgroup nursery, 6 within a hospital setting and 15 were listed as coming from other sources. There was some association with knowledge of the source of infection and a decision to provide preventative therapy. In 14% of cases where the infection was thought to derive from a home or school contact, preventative therapy was provided.

Vaccine efficacy

Vaccine efficacy was calculated using the screening method and is shown for each age group for each year and overall in Table 6. There was a significant downward trend in efficacy with increasing age from 95·8% in the 6–11 month age group to 75·8% in the 5–14 year age group ($t = 2{\cdot}44$, 95% CI {1·85–14·89}, $P < 0{\cdot}001$). Over the 3-year period studied, for the 6–11 month age group there was no evidence of a linear trend over time ($t = 0{\cdot}91$, 95% CI {0·38 to 2·2}, $P = 0{\cdot}82$) whereas for the 1–4 year olds there was a significant downward trend in efficacy ($t = 1{\cdot}6$, 95% CI {1·2–2·2}, $P = 0{\cdot}004$). The reason for this is not clear as all these children were exposed to the accelerated vaccination schedule at 2,3 and 4 months of age (introduced mid-1990) with the exception of some of those aged 4 years in 1995. For the 5–15 years old there was a downward trend with time. However, closer examination of the data showed that efficacy significantly dropped from 1995 to 1996 then rose from 1996 to 1997. Hence, the overall linear trend is not significant ($t = 1{\cdot}51$, 95% CI {0·49–4·6} $P = 0{\cdot}45$).

DISCUSSION

Some models of vaccine coverage, immunity, and protection against transmission have pointed to an expected lengthening of the inter-epidemic period in England and Wales, an expected constancy of incidence rates, and an increase in proportion of cases in older children and adults. The latter would, in turn, be exaggerated if efficacy declined substantially with age [14]. Conversely other authors, noting the absence of lengthening of the interepidemic curve in England despite good vaccine coverage, suggested that vaccination will only control disease and not circulation of *B. pertussis* [15]. The recent flattening of the pertussis incidence curve associated with increased vaccination coverage has made identification of

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epidemics more difficult but if a limited epidemic occurred in 1993/4 then the interepidemic period is relatively unchanged. There was an increase in the numbers of notifications in 1996 and 1997. However, early 1998 data (1253 notifications to end of week 40), suggests the increase although modest by historical proportions is already at a peak. This contrasts with some other countries with similar vaccination rates, the United States and the Netherlands, where recent substantial increases in pertussis have been described [4, 16]. In Scotland there were also increases in notifications in 1996/7 which were predicted to continue to 1998 and have since declined [17, 18]. A recent local review identified the presence of significant under notification. However, this was also identified in the United States and the Netherlands and would not account for the altered patterns of disease recently [4, 16, 19].

The age distribution of notifications in England has been described as changing in line with predictions from modelling although the proportion occurring in individuals aged 5 years and over was consistently lower than predicted [14]. The trend to increasing notifications in both those too young for vaccination [6], and in older persons many years post vaccination and without the benefit of natural boosting, continued over the 3 study years. While a larger proportion of notifications in those aged over 15 years and a larger recent increase in actual numbers would be expected, case ascertainment is known to be lower during non-epidemic times and among vaccinated persons [20] and proportionately lower in older groups where the presentation is often atypical as chronic cough and lymphocytosis tend to be absent [21].

The provision of preventative antibiotics prior to disease onset was associated with a reduction in the severity of the attack among laboratory confirmed cases, the majority of whom were young infants. In contrast a recent review found little evidence of clinical benefit from erythromycin prophylaxis given to home/residential care contacts [22]. However, few of the contacts in the studies in that review were very young infants. The single study in neonates showed stronger evidence of clinical benefit from erythromycin prophylaxis of infants whose mothers develop pertussis around term, combined with erythromycin treatment of the mother [23]. The review recommended its use, in England, for household contacts of cases particularly those not fully vaccinated and at most risk [22]. While our dataset is skewed toward younger and more severely ill cases, and only a small proportion actually received prophylactic antibiotics, the protective association was robust and worth highlighting to primary care physicians.

The limitations associated with the use of the screening method for vaccine efficacy and the potential to overestimate efficacy have previously been described [24]. Since it is more difficult to culture the organism in vaccinated than unvaccinated children with pertussis, efficacy estimates derived for bacteriologically confirmed cases are likely to overestimate true vaccine efficacy [25]. The efficacy rate remained over 90% in children under 5 years of age during the study period. However, there was a substantial decline in efficacy with age, falling to around 75% in older age groups. The importance of pertussis in older age groups sustaining transmission, and in acting as a source of infection for young requires further study. The fall off in efficacy over the period 1995–7 in 1–4 year olds is difficult to interpret. While this may represent increasing ascertainment in years when case numbers were higher [20], it may also be an early indication of a more rapid decline in efficacy with lack of boosting from reduced exposure to circulating *Bordetella pertussis* in recent years.

As with a number of recent international reports from the United States and Australia [1, 3, 26, 27] our data show a significant recent mortality in very young children affected by pertussis and an increasing proportion of cases in very young children. In the presence of continued high vaccination levels, and early signs of more rapid waning of the efficacy of whole cell vaccine under an accelerated program, high levels of morbidity and mortality in young children can only be addressed by providing booster vaccination in older groups [6, 7, 24] and increased recognition of disease in milder forms so that those at risk of severe disease can be given antibiotics at an early stage.

Independent of vaccination status or age, disease caused by serotype 1,2 was more likely to be associated with complications and admission to hospital. Altered severity associated with serotype of *B. pertussis* has not previously been described and the recording of complications and admission to hospital in the enhanced surveillance database was not complete. However, the significance of the association was strong in multivariated models and increased with increasing time and data points.

Historical data from the United Kingdom suggested that the highly fimbriated serotype 1,2 became more predominant as a cause of disease during times of low

vaccine uptake and was seen more commonly in unvaccinated children, plausibly because whole cell pertussis vaccine had less efficacy against serotype 1,3 [14, 24, 28–31]. Similar findings were available from a Swedish review where the proportion due to 1,2 increased since whole cell vaccine was ceased in 1979 and from a comparison of UK and German data [32, 33]. Our data from the period 1995–7 involves a greater number of interepidemic cases and casts doubt on these assumptions. At a time of continued high vaccination coverage, the proportion of cases due to serotype 1,2 is increasing independently of the vaccination status or age distribution of cases. In the Netherlands the recent 10-fold increase in pertussis incidence, which has occurred despite continuing high coverage with whole cell vaccine, has been associated with an increase in serotype 1,2. (F. Mooi, personal communication). However, cyclic patterns in serotype frequency have occurred in the past in the Netherlands, unrelated to changes in pertussis incidence [34] and it has been postulated that changes in pertactin subtype may be associated with the recent re-emergence of pertussis in the Netherlands [35]. The relationship between the genetic loci determining virulence, pertactin subtypes and fimbrial antigens merits further study.

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