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Age-specific efficacy of pertussis vaccine during epidemic and non-epidemic periods

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SUMMARY

A national survey was conducted of 3150 notified cases of whooping cough in order to determine age-specific pertussis vaccine efficacy by the 'screening' method. The cases were collected over two periods, one just prior to the start and one at the first peak of the whooping cough epidemic of 1989–90. Vaccination status was determined by a postal questionnaire to the reporting doctor and clinical data were also collected to provide efficacy estimates according to standardized case definitions. Overall, observed vaccine efficacy was high but differed between epidemic (87%) and non-epidemic (93%) periods ($P = 0{\cdot}03$). Efficacy estimates were generally higher for typical or severe cases than for children with an atypical illness. Vaccine efficacy declined with age ($P < 0{\cdot}01$) but estimates remained high up to the age of 8 years. This study will provide baseline data for comparison with efficacy observed from similar studies of children immunized at an accelerated schedule and from phase III studies of acellular pertussis vaccines performed elsewhere.

INTRODUCTION

In May 1990, an accelerated schedule of primary vaccination with combined diphtheria–tetanus–pertussis vaccine at 2, 3 and 4 months of age was introduced in the UK [1]. Although studies have shown no major differences in pertussis antibody levels in children immunized with accelerated and prolonged schedules [2, 3], the absence of an antibody correlate of protection for pertussis will necessitate the field evaluation of vaccine efficacy in the future. It will be of particular importance to compare age-specific estimates of vaccine efficacy in children immunized according to the prolonged schedule with those obtained after the introduction of accelerated immunization. In addition, such estimates can be compared with those for acellular pertussis vaccines obtained from phase III studies conducted in other countries [4, 5].

National estimates of pertussis vaccine efficacy were last obtained in the whooping cough epidemic of 1978–80 [6]. The overall efficacy was 82% for all notified cases, but substantial variation occurred when cases were defined

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according to additional clinical and laboratory criteria. There was no evidence of a decline in age-specific vaccine efficacy in children up to 4 years after vaccination [6], although a smaller study has suggested that efficacy may decline to 46% by the seventh year after vaccination [7].

A national study was conducted with the aim of providing baseline efficacy estimates for the current United Kingdom whole-cell pertussis vaccine. The estimates can then be compared with those obtained with immunization at an accelerated schedule or in clinical trials of acellular pertussis vaccines. The objectives of the study were to describe the current clinical and laboratory features of notified cases and to obtain age-specific estimates of whole-cell pertussis vaccine efficacy in children up to 9 years of age according to standardized case definitions. As there is evidence that the proportion of whooping cough cases which are notified varies with disease incidence [8, 9], efficacy estimates were determined for two study periods, one just prior to the onset and the second at the first peak of the epidemic of 1989–90.

METHODS

The study was coordinated by the Communicable Disease Surveillance Centre (CDSC) and conducted through the Medical Officers of Environmental Health (MOsEH). These officers receive statutory notifications of whooping cough from reporting doctors via their local authority and summarize this information on a weekly basis for the Office of Population Censuses and Surveys (OPCS). Upon publication of the weekly figures by OPCS, the MOEH was sent a coded questionnaire for each notified case of whooping cough. The MOEH then forwarded the questionnaire to the reporting doctor who was asked to complete the clinical details and vaccination status of the child and to return it to CDSC. Where no reply was received after 8 weeks, a duplicate form was sent to the MOEH. No patient-identifying information was collected at CDSC. The survey was carried out during OPCS weeks 10–26 and 45–48.

Vaccine efficacy

For the calculation of vaccine efficacy the 'screening' method was employed whereby estimates are derived using the following equation [10]:

$$\text{Vaccine efficacy (\%)} = 100 \times \frac{[\text{PPV} - \text{PCV}]}{\text{PPV}[1 - \text{PCV}]},$$

where PPV is the proportion of the population that has been vaccinated and PCV is the proportion of the cases occurring in vaccinated individuals. For the determination of PCV, cases occurring in partly vaccinated children and in children with unknown vaccination status were excluded. For children aged 1–4 years, the proportion of the population vaccinated (PPV) was derived from the national vaccine coverage rate for England and Wales obtained from the Cover of Vaccinations Evaluated Rapidly (COVER) scheme [11]. For children aged 5–9 years the proportion of the population vaccinated (PPV) was obtained from Department of Health statistics.

Case definition

For the purposes of clinical trials the World Health Organisation has recommended a case definition for pertussis including clinical criteria plus either laboratory confirmation or evidence of contact with a confirmed case [12]. In routine practice and in particular amongst vaccinated cases, the isolation of *Bordetella pertussis* has a low sensitivity [13]. Because of this the case definitions used in this study were based only upon the clinical component of the WHO definition, that is 21 days or more of paroxysmal cough. Analysis of efficacy was performed for any notified case, for cases with 3 or more weeks of paroxysmal cough, and for atypical cases which had either non-paroxysmal coughing or where the coughing did not persist for 3 weeks. In addition, efficacy estimates were obtained for cases with 3 or more weeks of paroxysmal cough in combination with either whooping or vomiting, for cases admitted to hospital and for those which were bacteriologically confirmed.

Statistical analysis

Proportions of children with specific clinical features were compared using a Mantel Haentsel adjusted chi-squared test after stratification, where appropriate, by age, vaccination status and study period. Logistic regression was used to obtain vaccine efficacy estimates and to investigate variations in efficacy with age, study period and clinical features. Confidence intervals for summary efficacy estimates in children aged 1–4 years for each study period were calculated after adjusting the models for overdispersion.

RESULTS

Totals of 2313 and 1720 provisional notifications of whooping cough were reported by OPCS during the weeks 10–26 and 45–48 of 1989 respectively. In the first period, notifications of pertussis were lower (mean weekly total 136, range 86–222) than in the second period (mean weekly total 430, range 310–549). Of 4033 cases notified to OPCS, in 40 cases the MOEH was unable to co-operate with the study, in 46 the notification or the reporting doctor could not be traced, in 34 the diagnosis had been changed, and in 12 the form was a duplicate. Questionnaires were sent to reporting doctors in the remaining 3901 (97%) notifications and completed replies were received for 3150/3901 (81%).

Of the 3150 cases for whom questionnaires were completed, 1652 (52%) were female and 1461 (47%) were male with 37 (1%) unspecified. Only 334 (11%) were in children aged less than 1 year, with 1422 (45%) aged 1–4 years, 1095 (35%) 5–9 years, 282 (9%) above 9 years and 17 (0·5%) of unspecified age. The age and sex breakdown of the cases in the study was the same as that for all notifications in 1989.

Of 2517 cases in children aged 1–9 years, 119 (5%) had unknown vaccination status, 1819 (72%) were unvaccinated, 131 (5%) were partly vaccinated and 426 (17%) were fully vaccinated. A further 22 (1%) cases were reported in children known to be vaccinated but where the number of doses was unspecified. For calculating efficacy these cases were distributed between fully and partly

Table 1. *Clinical characteristics reported in notified whooping cough*

Clinical characteristics	Aged 1–4 years		Aged 5–9 years	
	Fully vaccinated ($n = 276$)	Unvaccinated ($n = 989$)	Fully vaccinated ($n = 150$)	Unvaccinated ($n = 830$)
Paroxysmal cough	221/232 (95%)	807/827 (98%)	127/131 (97%)	680/699 (97%)
Paroxysmal cough ⩾ 3 weeks	148/205 (72%)	571/723 (79%)	107/119 (90%)	544/636 (86%)
Paroxysmal cough ⩾ 3 weeks with vomiting	111/187 (59%)	470/672 (70%)	78/110 (71%)	435/585 (74%)
Paroxysmal cough ⩾ 3 weeks with whooping	76/183 (42%)	355/664 (53%)	59/109 (54%)	332/590 (56%)
Admitted to hospital	5/274 (1.8%)	71/975 (7.3%)	2/148 (1.3%)	34/816 (4.2%)

Denominators are those cases in which the questions were answered.

vaccinated groups in the same proportions as for those vaccinated children where the number of doses had been specified.

Clinical characteristics

The signs and symptoms reported from unvaccinated and fully vaccinated children are shown in Table 1. For all clinical categories which included paroxysmal cough a substantial proportion of cases could not be classified because the doctor had failed to complete the question on number of paroxysms. In respect of other features included in the table completion rate for each question was high (83–99%) and was similar in epidemic and non-epidemic periods. Because of the poor response to the question on paroxysmal cough, 8 weeks into the study, the wording of the questionnaire was simplified. Following the amendment the response for this question improved to over 93% and was similar in epidemic and non-epidemic periods. Of the cases with complete data the proportion with each of the clinical features was similar before and after the change in the questionnaire. Because of this it was felt to be valid to include cases with complete data collected from the first 8 weeks of the study.

Unvaccinated children had a more typical and severe illness than fully vaccinated children. A significantly higher proportion of unvaccinated children required hospital admission ($P = 0{\cdot}0004$), or had a prolonged paroxysmal cough (for 3 or more weeks) with whooping ($P = 0{\cdot}025$) or with vomiting ($P = 0{\cdot}023$). Older children also had a more typical illness, a higher proportion of the older cases were reported to have a prolonged paroxysmal cough ($P = 0{\cdot}000\,01$), or such a cough with associated vomiting ($P = 0{\cdot}018$) than in the younger group (Table 1). However, when judged by rates of admission to hospital, the illness was less severe in the older than the younger group ($P = 0{\cdot}006$).

The characteristics of the whooping cough illness differed in the two periods covered. Amongst children aged 1–9 years with complete data, 567/741 (76%) had a prolonged paroxysmal cough with vomiting during the non-epidemic period compared to 527/813 (65%) in the epidemic period ($P = 0{\cdot}000\,002$).

Table 2. *Efficacy of pertussis vaccine by case definition in children aged 1–4 years*

Case definition		Vaccine efficacy % (95% confidence interval)	
		Non-epidemic period	Epidemic period
Any notified case		93 (89–95)	87 (82–91)
Atypical case*		92 (80–97)	83 (68–91)
Case with paroxysmal cough ⩾ 3 weeks	Any case	94 (91–96)	89 (85–92)
	With vomiting	94 (91–96)	90 (87–93)
	With whooping	95 (93–97)	90 (86–93)

* With non-paroxysmal cough or with paroxysmal cough for < 3 weeks.

Table 3. *Efficacy of pertussis vaccine by age (for notified cases with paroxysmal cough for 3 or more weeks)*

Age in years	Proportion of the population vaccinated	Vaccine efficacy (%)	
		Non-epidemic period	Epidemic period
1	0·82	95	94
2	0·76	92	88
3	0·73	93	86
4	0·70	93	87
5	0·68	90	93
6	0·65	95	84
7	0·64	91	79
8	0·58	85	85
9	0·52	78	48

Of 1819 cases reported in unvaccinated children aged between 1 and 9 years, culture of specimens was performed in 203 and *Bordetella pertussis* isolated in 107 (53%). Amongst 426 vaccinated children of the same age only 20 specimens were taken for culture and *Bordetella pertussis* was isolated in 7 (35%).

Vaccine efficacy

Summary vaccine efficacy estimates, in children aged 1–4 years, based upon various clinical case definitions are shown in Table 2. Vaccine efficacy was generally lower in the epidemic than in the non-epidemic period, being 87% as opposed to 93% for all notified cases in this age group ($P = 0{\cdot}03$). Efficacy was high for the more typical cases, those with prolonged paroxysmal cough with and without additional features, and in those with severe disease. Efficacy was 98% for cases admitted to hospital (95% confidence interval 90–100%) and 97% (95% confidence interval 93–99%) for cases which were bacteriologically confirmed (the data for the two study periods were combined because of small numbers).

As the clinical features of notified cases vary with age (Table 1) and because efficacy varies with case definition (Table 2), comparison of age-specific efficacy was made for cases meeting a standard case definition of 3 or more weeks of paroxysmal cough. Summary age-specific efficacy estimates for each period in children up to the age of 9 years are shown in Table 3. Efficacy remained high up to the age of 8 years, but overall, there was evidence of a downward trend in efficacy with age ($P < 0{\cdot}01$).

DISCUSSION

The signs and symptoms of notified whooping cough in this study are similar to those reported previously. The majority of patients have a paroxysmal cough for 3 or more weeks [14, 15], with vomiting and whooping being commonly associated symptoms [16]. We also confirmed the findings of previous studies that the illness is more severe in unvaccinated than vaccinated children when judged by rates of admission to hospital [14–16]. As previously described, the illness is less typical in fully vaccinated children [15–17] with the presence of associated vomiting and whooping being less common than in unvaccinated cases.

The efficacy estimates derived in this study are higher than in the national study of 1978–80; the observed efficacy of 87% (in children aged 1–4 years) during the epidemic period of our study compares to an observed efficacy of 82% (in children aged 1–6 years) in 1978–80 [6]. In a small study of cases identified during a local outbreak in 1986–7, efficacy was 87% for notified cases but fell to 75% when cases of a similar illness ascertained by parental questionnaire were included [18]. This fall was attributed to a tendency for doctors to under-report cases in vaccinated children [18], and suggests that this selective under-reporting forms a major bias in the derivation of efficacy estimates from notifications. In addition, there is evidence that notification efficiency increased during the resurgence of whooping cough in the late 1970s [8, 9]. As the increase occurred amongst milder cases [8], and because the illness is less severe in immunized children [14–16], reporting of cases in immunized children may increase with increasing whooping cough incidence. This would produce a fall in estimated efficacy and is consistent with the finding that the estimates obtained were consistently lower during the epidemic period of our study. Alternatively, the lower efficacy observed during the epidemic period may reflect poorer protection from vaccination in the face of heavy exposure, a theory which is supported by the low estimates of vaccine efficacy obtained amongst household contacts [6].

Other possible biases involved in using the screening method to calculate efficacy have been well described [19, 20]. A study of a local outbreak which calculated efficacy by both the screening method and from direct attack rates in the population obtained estimates of 87 and 88% respectively [18]. Unlike the latter study, however, efficacy estimates in our study are obtained from national vaccine coverage rates which do not take account of local variation. Unvaccinated children are more likely to come from areas with low vaccine coverage, where pertussis may circulate more freely, and may therefore be more commonly exposed to infection. If such variation occurs, the use of national coverage data could produce artificially high efficacy estimates [19], particularly during periods of low whooping cough incidence.

Another problem arises because children who had whooping cough prior to the study period are included in the analysis. These non-susceptible children would be expected to form a higher proportion of the unvaccinated than the vaccinated group, particularly amongst older children. It can be shown that as a consequence of this, when calculating age-specific efficacy by the screening method, a fall in efficacy with age may be observed, even if the protective effect of the vaccine remains constant [21]. Despite this, it is reassuring that estimated efficacy remains

high up to 8 years of age. The decline in efficacy at 9 years of age in the epidemic period is similar to that reported previously [2].

This study confirms the finding that the efficacy of the pertussis vaccine depends upon case definition and that the majority of notified cases in England and Wales consist of 3 or more weeks of paroxysmal cough. Even during the epidemic period, our data imply that whole-cell pertussis vaccine protects well against such an illness, with an observed efficacy of 89% amongst children aged 1–4 years. This represents the only data available for comparison with the efficacy of 41% which was demonstrated amongst cases meeting the same case definition in a phase III trial of acellular pertussis vaccine [5]. It is planned to repeat this study to obtain age-specific efficacy estimates for cohorts of children who have received accelerated immunization and to assess whether protection declines at an earlier age than with a prolonged schedule. If so, the inclusion of pertussis in the pre-school booster should be considered. A study to document reactions and antibody response to pre-school vaccines with and without the pertussis component is currently being conducted.

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