Archives of Disease in Childhood 1991; **66**: 854–857

Vaccine efficacy and control measures in pertussis

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Abstract

An outbreak of pertussis in primary schoolchildren in the St David's area of Pembrokeshire provided the opportunity to estimate pertussis vaccine efficacy. The estimate of efficacy was 88% when notified cases were used, but this fell to 68% when all children with bouts of coughing for two or more weeks were included. Notified cases were significantly less likely to have been vaccinated than other cases with similar symptoms. Therefore vaccine efficacy estimates based upon notified cases are likely to be biased. However, even the lower estimates suggest that pertussis immunisation is highly desirable and efforts to improve coverage should be increased.

Public anxiety about the safety and efficacy of pertussis vaccine in the United Kingdom in the 1970s led to a sharp fall in vaccine uptake and a consequent increase in the severity of pertussis epidemics in 1977/9 and 1981/3.[1] Fears about the safety of the whole cell vaccine have been addressed, but there is a continuing need to monitor vaccine efficacy, both for pertussis and other routinely administered vaccines.[2]

Measurement of vaccine efficacy requires the comparison of disease experience in vaccinated and unvaccinated children in a population in which both groups are equally exposed to the agent.[3] Outbreaks present such opportunities to carry out field evaluation of vaccine efficacy. In an outbreak of pertussis centred on a primary school in the St David's area of Pembrokeshire in 1987 vaccine efficacy was measured and the use of the accelerated schedule for vaccine delivery was evaluated.[4]

Methods

Vaccination status of all children in the study was determined from health authority records and only children with documented completed vaccination were considered to have been vaccinated for the purposes of the study. Children receiving only one or two doses of vaccine were excluded from estimates of vaccine efficacy.

Pernasal swabs were sought from notified cases, transported in charcoal media, and plated out within 12 hours on selective medium. General practitioners were asked to obtain pernasal swabs on new cases, or if that was not possible to take cough plates.

All cases of pertussis occurring in children in the two practices covering the St David's area from January 1987 to June 1987 were sought as follows. All preschool children registered in the practices were identified by the attached health visitor, families were contacted, and children who had a history of cough for two or more weeks were identified. A letter and questionnaire were sent to parents of all children in primary and secondary schools in the St Davids/Solva area on 2 June. Parents reporting illnesses in children were interviewed by the health visitor.

A *notified case* was a case formally reported by a doctor to the local authority. A *probable* case was a child with bouts of coughing lasting for two or more weeks with bouts followed by vomiting, whooping, or choking/blue colour but who was not a notified case. A *possible* case was a child with bouts of coughing for two or more weeks but without vomiting, whooping, choking or turning blue and who was not notified. Statistical comparisons were carried out by χ^2 test, t test, and the Mann-Whitney test.

Vaccine efficacy was estimated by three methods for a cohort of children born between 1 January 1981 and 31 December 1985 registered in the two practices and identified from the child health register.

(1) Screening method

$$PCV=\frac{PPV-(PPV\times VE)}{1-(PPV\times VE)}$$

Where PCV=proportion of cases vaccinated, PPV=proportion of population vaccinated, and VE=vaccine efficacy.

(2) Direct population estimates

$$VE=\frac{AR\ unvaccinated-AR\ vaccinated}{AR\ unvaccinated}$$

Where AR=attack rate and VE=vaccine efficacy.

(3) Secondary household attack rates

Using the method of (2) above, attack rates in vaccinated and unvaccinated household contacts who were contacts of notified or probable cases were calculated. A secondary household case was a child meeting the case definition of a notified or a probable case who developed symptoms 4–30 days after a prior notified or probable case living in the same household.

Confidence intervals (CI) for estimates of vaccine efficacy were calculated through a logarithmic transformation method as described by Katz *et al.*[5]

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Accepted 22 March 1991

CONTROL MEASURES

The recommended schedule of childhood immunisation in Pembrokeshire was changed in June 1987 to the rapid schedule of three doses at intervals of one month starting at 3 months of age.[4] All children aged 1–7 years not having completed pertussis immunisation were identified via the child health computer register and a list sent to general practitioners and health visitors so that the children could be offered vaccination. Evaluation of the success of this policy was attempted by estimating the coverage of completed vaccination against pertussis using the child health system. A letter was sent to all general practitioners by the chief administrative medical officer on 1 June 1987 informing them of the outbreak and the changed schedule. We recommended that children suspected to have pertussis or who were contacts of known cases who developed a cough should be excluded from school for the first three weeks of illness or until they had received five days of a 10 day course of erythromycin.

Results

CLINICAL FEATURES

Forty two cases of pertussis were notified in Pembrokeshire between January and June 1987, 31 of which were from the two practices in St David's/Solva. There had been no notifications from these practices since before 1984 even though in 1986 there were 88 notifications in Pembrokeshire. *Bordetella pertussis* was isolated from one cough plate and from one of 23 pernasal swabs, although all were taken three or more weeks after onset. Additionally, 59 children in these practices met the case definition of probable cases and 44 were possible cases (table). One non-notified probable case was admitted to hospital and *B pertussis* was identified from sputum culture.

Notified cases were more likely than probable cases to have a cough followed by whooping, although when children less than 8 years of age were considered slightly more of the non-notified probable cases reported whooping (63% compared with 59%). Notified cases had a slightly longer mean duration of cough than probable and possible cases (8·5 weeks compared with 6·2 weeks, p=0·01) and lost more days from school (7·4 days compared with 4·4 days, p<0·01). Although the median number of bouts of coughing were the same, the mean for notified cases (3·7) was significantly greater than for the others (3·2, p<0·01). Probable and possible cases were almost twice as likely as notified cases to have had a completed course of pertussis immunisation (p<0·05).

VACCINE EFFICACY

(1) Screening method

In children aged 1–6 years living in Pembrokeshire five of 30 notified cases (17%) and 65·5% of the cohort were vaccinated, giving an efficacy estimate of 90% (95% CI=83 to 93%). In the two practices in the St David's area five of 24 notified cases, 11 of 22 probable cases, and nine of 17 possible cases were vaccinated. Vaccination records were missing for one probable case and two possible cases. The vaccine coverage for this cohort was 67·6%. The vaccine efficacy based upon notified cases alone, notified and probable cases, and all cases (notified, probable, and possible cases) respectively was 87% (79 to 92%), 74% (60 to 84%), and 71% (56 to 80%).

(2) Direct population estimates

In the two practices there were 175 vaccinated children aged 1–6 years of whom five were notified cases, 11 were probable cases, and nine were possible cases. Seventy three children were unvaccinated of whom 17 were notified cases, 10 were probable cases, and six were possible cases. Eleven children were incompletely vaccinated, of whom two were notified cases. Vaccine efficacy for notified cases was 88% (68 to 95%) and for notified and probable cases it was 75% (56 to 89%). When all cases were included vaccine efficacy fell to 68% (51 to 80%).

(3) Secondary household attack rates

Only 20 household contacts aged 1–6 years were identified. Ten of 17 vaccinated children had a cough for two or more weeks as did two of three unvaccinated children. The numbers were too small to calculate vaccine efficacy.

Clinical features of children with a cough for two or more weeks

	Notified cases (n=31)	*Probable cases (n=59)*	*Possible cases (n=44)*
Mean (SD) age (years)	5·4 (2·0)	7·3 (3·3)	7·7 (3·9)
No (%) who completed vaccination	7 (23)	25 (42)	21 (48)
No (%) with cough:			
Worse at night	23 (74)	44 (75)	32 (73)
Followed by:			
Vomiting	23 (74)	40 (68)	0
Whooping	19 (61)	23 (39)	0
Choking	19 (61)	33 (56)	0
Provoked by:			
Exertion	22 (71)	39 (66)	7 (16)
Eating	8 (26)	6 (10)	0
Excitement	3 (10)	5 (8)	0
Median (range) duration (weeks)	8 (3–20)	6 (2–24)	4 (2–16)
Median (range) bouts of cough/day	4 (2–4)	4 (2–5)	3 (2–4)
No with complications:			
Fits	0	1	1
Hospital admission	0	1	1
Nosebleeds	1	3	0
Otitis media	1	0	1
Median (range) days school lost (age ≥4 years)	10 (0–20)	5 (0–20)	0 (0–20)

CONTROL MEASURES

In June 1987, 66% of the cohort of children living in Pembrokeshire who were born between 29 May 1981 and 31 December 1987 were recorded as having completed pertussis immunisation. This increased to 69% in July and 70% in August. Altogether 485 children, 6·5% of the total, had received only two doses by June. This number fell to 262 in July, 209 in August, and 176 by December. Thus 65% of children who had two doses were given the third protective dose within six months of the control recommendation and 46% within one month. This group accounted for all the improvement in vaccine uptake.

Discussion

The outbreak of pertussis in the St David's area occurred in an interepidemic year. The children in this relatively isolated area appear to have escaped the outbreak in Pembroke in the previous year. Transmission seems to have occurred mainly at the end of the winter school term so that children became ill over the school holiday. On return to school transmission resumed causing a second peak of cases four weeks into the term.

Fifteen percent of children up to 15 years of age were found to have a cough for two or more weeks in the spring of 1987, and 14% of children less than 8 years of age had notified or probable pertussis. The diagnosis of pertussis was confirmed bacteriologically in only three cases but the pernasal swabs were not taken from any of the children within three weeks of onset and therefore were unlikely to have a high yield of *B pertussis*. The clinical features of children with a cough lasting two or more weeks were typical of pertussis, and 67% met our epidemiological case definition which was similar to that used in other studies.[6] The prolonged duration of illness, with a median duration of cough of 6–8 weeks, emphasises the serious nature of pertussis.

Of the 90 cases with bouts of coughing for two or more weeks followed by whooping, vomiting, or choking/turning blue only 31 were formally notified. The symptoms in the non-notified probable cases were little different from the notified cases, although duration of cough was shorter; all but six had visited their doctor. Notified cases were younger and were less likely to be vaccinated. It is possible that notified cases presented features which more clearly suggested the diagnosis of pertussis than the non-notified probable cases but in the data we collected there was no evidence of this. Almost all the children went to the same primary school and were likely to have had the same infection. An alternative explanation is that cases were less likely to be diagnosed and notified as pertussis if they were known to have been vaccinated. Such a bias would result in an overestimation of vaccine efficacy based upon notified cases only: vaccine efficacy using notified cases was 13% greater than when both notified and non-notified probable cases were used.

Another factor to be considered in interpreting these data is that estimates of pertussis vaccine efficacy will be expected to increase as the severity of disease used as a case definition increases.[1 2] There are two reasons for this: firstly, severe cases are more likely to be true pertussis and secondly, pertussis vaccine is known to reduce the severity of pertussis even when it fails to prevent disease. However, our data suggested that though notified cases had a more prolonged illness, severity as measured by frequency of coughing and complications rate was similar to that in the probable cases. The 13% difference in efficacy would appear to be the result of the notification bias.

Vaccine estimates which included possible cases (that is, without whooping, vomiting, or choking) were 5% lower than when only notified and probable cases were used. The possible cases occurred mainly in the second term and another infection may have been circulating. If so vaccine efficacy would be underestimated by including these possible cases in the calculations.

The vaccine efficacy estimate of 80% calculated by Jenkinson from cumulative data on 1–7 year olds from 1970–86 was based upon diagnostic criteria of paroxysmal cough for three or more weeks 'usually associated with vomiting and often whooping'.[7] This case definition is closer to our notified and probable cases for which we had an efficacy of 75%, with 95% confidence intervals including Jenkinson's estimate. Thus we have no evidence of a decline in efficacy for pertussis vaccine. Our data set was not large enough to examine efficacy within narrower age bands.

Routine monitoring of vaccine efficacy is highly desirable for several reasons.[1 2] The prevailing antigenic composition of the disease organism may change causing a loss of vaccine efficacy. Different commercial vaccines and even batches of the same vaccine will not have identical efficacies and monitoring may help to identify problems in production. Incorrect storage and administration as well as changes to the recommended dose, timing, frequency, and age at vaccination may be associated with reduced efficacy. Furthermore, as vaccine cover improves the proportion of cases vaccinated will increase without any fall in the efficacy. This concept is not readily appreciated and continued demonstration of efficacy will be important in maintaining confidence in the vaccine. Locally generated estimates may be more persuasive than national data in local health promotion efforts. Various methods for estimating efficacy based upon locally generated data have been proposed for local use.[8] However, our data suggest that notifications may give significantly biased estimates. Where possible cohort and case-control studies should use unbiased samples of cases identified by active case searching.

The attempts to improve uptake of the third protective dose of pertussis vaccine in children under 8 years old in Pembrokeshire were reasonably successful. About half of the children who could have benefited from a single extra dose received it within a month. No improvement in uptake among never vaccinated children was observed. The new two, three, four month schedule for pertussis vaccine introduced in

1989 in the United Kingdom now makes the accelerated schedule for outbreaks redundant.

I would like to thank Dr J Ogle, Dr SA Hamilton, Dr GW Middleton, and Dr PG Gillam for their cooperation; Miss A Ayers and Miss Sue Stevens, the health visitors, for essential assistance in carrying out this survey; and Dr Paddy Farrington, CDSC, for statistical assistance. The outbreak was managed by Dr R F Doyle, chief administrative medical officer, Pembrokeshire Health Authority with considerable support from Mr Alan James. Dr Anne Bushell, consultant microbiologist, and microbiology department staff, Withybush Hospital carried out the microbiology.

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Did Alice have glandular fever?

Here's one to test your diagnostic acumen. Did you know about the relationship between metamorphopsia and infectious mononucleosis? As you know, metamorphopsia is a form of illusion in which the form, size, movement, or colour of objects is distorted. It has been related to lesions in the occipital lobes or in the occipitotemporal or occipitoparietal regions.

In children it may be caused by infectious mononucleosis. Three children so affected were described in 1977[1] and Lahat and colleagues have recently described a 6 year old girl from Israel (*Journal of Neurology, Neurosurgery, and Psychiatry* 1990;**53**:1104). The child described the visual illusions in association with mild headache coming on two weeks after the onset of glandular fever. The episodes lasted a few minutes each time and occurred several times a day. Cranial computed tomography was normal but an EEG showed sharp high voltage waves in the parieto-occipital region. Two weeks later the EEG was normal. The symptoms lasted for four weeks.

Metamorphopsia has been called the Alice in Wonderland syndrome.[2] Apparently it can come on before, with, or after the other features of glandular fever.

ARCHIVIST

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