Whooping-cough: Difficulties in Diagnosis and Ineffectiveness of Immunization

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In 1964, in general practice in Peeblesshire, we found that a type of paroxysmal cough had spread widely among the older children at one village school before a diagnosis of whooping-cough was made. Very few of the children were seen by their doctors in the earliest phase of this epidemic. Those affected were in the 8 to 12 age group and had not been immunized against pertussis.

In the children below the age of 8 years pertussis immunization was at this time believed by us to be virtually complete. (We subsequently discovered that 7 children out of 108 in this age group had had no immunization whatever against pertussis.) Because of this high immunization rate and because of the large proportion of older children already showing symptoms, the medical officer of health permitted cases and suspect cases to continue attending school unless the severity of their illness made it necessary for them to be absent.

When one or two of the immunized children developed similar coughs we saw an opportunity to study the effectiveness of the protection given by immunization. We therefore charted the subsequent spread of the infection through the families of the village. Advantage was taken of the fact that at this particular time a trainee assistant was attached to each of the two practices which provided medical services for this village.

The object of the study was to find out if the immunization which the family doctors had given prevented attacks of pertussis and limited its spread. Subsidiary objects were to act as a training exercise in the planning of research in general practice for the benefit of the trainee assistants and to assess the diagnostic value of pernasal swabs, since it was necessary to confirm that the causal organism was *Bordetella pertussis*.

Material and Method

All children below the age of 15 in the village and all other members of their households were studied (Table I). The last case of pertussis infection in this school was in 1954.

TABLE I.—*Population Studied*

	No.	Definite Previous History of Whooping-cough
Pre-school children	63	1 (2%)
Children attending local school (aged 5–12)	98	13 (13%)
Children attending other schools (aged 11–15)	38	16 (42%)
All other members of these households over 15 years	209	96 (46%)
	408	126 (31%)

After cases suggestive of pertussis infection had been noted among the immunized children a visiting-list was drawn up of all families in the village having children. These were visited at weekly intervals for at least four weeks for the purpose of recording the presence and spread of the illness. The following information was recorded for all members of each family: (1) the presence of a cough of any type; (2) cough occurring during the day in paroxysms—which were interpreted for this study as four or more coughs in close succession; (3) cough occurring during the night in paroxysms; (4) a cough of greater duration than two weeks; (5) vomiting following coughing; (6) a history of whoop; (7) haemorrhagic complications of the paroxysms; and (8) past history of whooping-cough. In addition, records were made of the treatment given, of bacteriological culture where this was done, and of immunization against pertussis.

Time Sequence of this Outbreak and Study

The first case was diagnosed clinically as whooping-cough on 16 February 1964. The next day the headmaster gave one of us the following information about his older schoolchildren:

Total Children in Classes Aged 8–12	No. of These Coughing	No. With Severe Cough	Known to Have Vomited	Absent from School	Previously Seen by Family Doctor
53	28	13	4	4	1

The medical officer of health was informed by telephone of this evidence suggesting an epidemic of pertussis.

By 5 March—according to information provided by the school teachers—39 of the children aged 8 to 12 had coughs. However, only 20 of those who were coughing had been seen by their family doctor. There were also five children with coughs in the 5 to 8 age-group classes; but on 26 March, when the school closed for Easter, 24 out of 45 children in this age group were coughing.

Visiting of all the families was begun during the week beginning 16 March and ended in the week beginning 13 April. By this time the epidemic was obviously waning, but families were requested to report any subsequent cases.

In our previous experience elsewhere we had not succeeded in making a bacteriological diagnosis of pertussis in suspected cases. However, attempts were made after 16 March to undertake a positive identification of the organism responsible for this outbreak, and the first cultures of *Bord. pertussis* were reported from pernasal swabs taken on 17 March. Cough-plates used at the same time on these patients were negative.

Symptoms

Of the 408 persons in the study 184 had a cough of some sort during or immediately prior to the investigation. It is not claimed that all 184 had whooping-cough. Our aim was to record the presence and spread of coughing throughout the community. From Table II different standards of clinical diagnostic criteria can be selected. These can be classified most simply as "suspected"—the development of a cough in a patient known to be exposed to the infection; "presumptive"—a paroxysmal cough in the same circumstances; and

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"definite"—a clear history of whooping after a paroxysm of coughing.

Since the symptomatology could have been influenced by treatment with tetracycline the numbers of patients receiving this treatment are also indicated in Table II.

TABLE II.—*Distribution of Symptoms from Patients with a Cough Compared with Those from Patients Having a Paroxysmal Cough (Shown in Parentheses) During the Epidemic*

	Pre-school Children	Local School	Other Schools	Over 15	Total All Cases
Cough of any type	36	72	19	57	184
(paroxysmal cough only)	(25)	(52)	(15)	(33)	(125)
Paroxysms Day	24	49	15	29	117
Paroxysms Night	13	34	12	20	79
Duration over 2 weeks	19	50	16	36	121
(paroxysmal cough only)	(19)	(40)	(13)	(26)	(98)
Vomiting	11	19	5	9	44
(paroxysmal cough only)	(11)	(16)	(5)	(8)	(40)
Whooping	4	14	3	6	27
(paroxysmal cough only)	(4)	(14)	(3)	(6)	(27)
Haemorrhage	2	7	2	4	15
(paroxysmal cough only)	(2)	(5)	(1)	(4)	(12)
Past history of pertussis	0	11	5	21	37
(paroxysmal cough only)	(0)	(6)	(3)	(14)	(23)
Tetracycline treatment	20	13	4	10	47
(paroxysmal cough only)	(17)	(13)	(4)	(10)	(44)
Total population studied	63	98	38	209	408

Immunization

When the immunization records were scrutinized some were found to vary from the recommended timing and number of injections. For example, some children over 3 had not yet had a fourth injection after three in infancy, and some over 5 had not yet had a fifth injection. These are excluded from Table III, as are a small number who had moved from other areas without adequate records of dates of immunization. Table III therefore refers only to those we considered to have completely satisfactory immunization. The M.R.C. Report on Vaccination against Whooping-cough (1956) states that, "Vaccines . . . gave substantial protection, which was maintained for at least two and a half to three years after vaccination." Since the recommended age for the fourth injection has now been altered from 2½ years to 18 months it is interesting to compare those aged less than 2 years with those aged 2 to 3 (Table III). Attention is drawn to the unsatisfactory picture presented by those aged over 5 years (Table III).

TABLE III.—*Distribution of Symptoms in Children Fully Immunized Against Pertussis*

	Total No.	Any Cough	Paroxysms: Day	Paroxysms: Night	Duration 2 Weeks	Vomiting	Whooping	Haemorrhage	Past History of Pertussis	Tetracycline Treatment
Age less than 2 with 3 injections	15	7	1	Nil		Nil	Nil	Nil	Nil	3
Age 2–3 with 3 injections	10	8	5	3	3	2	2	Nil	Nil	3
Age less than 5 with 4 injections	15	7	3	2	3	1	2	Nil	1	1
Age over 5 with 5 injections	33	22	17	10	15	6	3	2	1	8
Total immunized	73	44	26	15	25	9	7	2	2	15

The numbers of children showing cough and paroxysmal cough may be extracted from Tables II and III and be given as percentages to demonstrate the effects of immunization (Table IV).

TABLE IV.—*Attack Rate in Relation to Immunization*

Group	All Children		Fully Immunized		Partially or Non-immunized	
	Cough	Paroxysms	Cough	Paroxysms	Cough	Paroxysms
Pre-school	57%	40%	55%	22%	61%	70%
Local school	73%	53%	67%	52%	77%	53%

By selecting paroxysms as "presumptive" evidence of pertussis infection a reduction in frequency is demonstrated in the fully immunized child in the pre-school group. There is no corresponding reduction in the number of these children "suspected" because they had a cough during the epidemic. The observations on the children attending the local school show all too clearly that immunization had very little effect on coughing and none at all on paroxysms.

It may also be noted at this point that 11 (85%) of the 13 children at the local school who had previously had whooping-cough developed cough during this epidemic. Six (46%) of these had a paroxysmal cough. A smaller proportion of those over the age of 15 with a previous history of whooping-cough also developed a cough (22%) or a paroxysmal cough (14%). A previous attack therefore gave no adequate protection.

Bacteriological Studies

Our laboratory was very successful in culturing *Bord. pertussis* from pernasal swabs in the first few days of these studies, but subsequently failed to maintain this high positive-culture rate. Swabs were taken exclusively in the first fortnight of the illness to increase the chances of a positive culture, and all were in the laboratory within four hours. All were taken before any antibiotics were prescribed. Pernasal swabs were also used for suspected cases in our practices outside the community studied.

We were unable to relate positive cultures for *Bord. pertussis* to severity of illness or to lack of previous immunization. All four doctors concerned obtained positive cultures. The dates of positive cultures from all pernasal swabs submitted over a four-month period show the initial success and subsequent poor results:

Dates of Positive Cultures for Bordetella Pertussis

	Positive	Negative
16 March (first swab sent)	0	1
17 March	5	0
18 March	2	1
19 March	0	4
20 March	0	5
28 March	1	
2 April	1	
18 April	1	
16 May	1	Various dates 81
Total (16 March to 13 July)	11	92

Detailed Bacteriological Results From the Community Studied

	Negative	*Bord. pertussis*	Pneumo-coccus	Staphylo-coccus	Total
Pernasal swabs	32	8	11	3	53

Distribution of Symptoms in Cases with Positive Culture

Total	Cough	Paroxysms: Day	Paroxysms: Night	Duration 2 Weeks	Vomiting	Whooping	Haemorrhage	Previous History	Tetracycline
8	8	7	8	8	4	3	2	2	2

Cough-plates were taken in addition to pernasal swabs in the first 19 cases from which culture was attempted. Their use was discontinued because most failed to give positive results. Some gave scanty growth with much contamination, whereas cultures from swabs taken at the same time gave a profuse growth.

Results of Cultures from Suspected Cases Outside the Community Described

	Negative	*B. pertussis*	Pneumo-coccus	Staphylo-coccus	*H. influenzae*	Haem. Strep.	Total
Pernasal swabs	37	3	8	2	1	3	50

The *Bord. pertussis* isolated was sensitive to streptomycin, tetracycline, chloramphenicol, and erythromycin. The organism gave positive agglutination reactions with *Bord. pertussis* serum and negative reactions with *Bord. parapertussis*. It was found to contain only type 1,3 agglutinogen.

Mode of Spread of Infection

Some authorities consider that babies should be screened from pertussis infection by the immunization of the older children in the family (Ramsey, 1961). We were quite satisfied that this epidemic had spread from the schoolchildren to the other members of the households. This included spread by fully immunized children.

From our records of the spread of this infection it was possible to ascertain which member of the family was the primary case. We have tabulated this (Table V) for the 184 patients with coughs listed in Table II.

TABLE V.—*Spread of Coughs Within Families During an Epidemic*

Group	Total Cases	Only Case in Family	Multiple Cases in Family	
			Primary Case	Secondary Case
Pre-school	36	5	2	29
Local school	72	14	36	22
Other school	19	5	6	8
Over 15 years	57	5	4	48
	184	29	48	107

It is evident that the infection was introduced into the majority of families by children attending the local school. In one family especially the spread of the infection from a fully immunized schoolchild to other members of the household was very clearly demonstrated as follows.

A 6-year-old schoolgirl fully immunized with five injections had a paroxysmal cough of over two weeks' duration with vomiting and whoop (onset 28 February 1964) prior to our bacteriological study. Her sister aged 4 (fully immunized, five injections) had a cough for one week (onset 10 March) and gave one of the first positive cultures (taken on 17 March). Their father, aged 36, developed a similar cough on 22 March, and a culture taken six days later was positive. A grandmother, aged 69, living in another home in the village but having close and regular contact with the above family developed the cough on 22 March, and from her also a positive culture was obtained (2 April). The mother remained symptom-free until 27 May, when she developed a paroxysmal cough of the same type as the rest of the family. Culture in this case was negative. None of the members of this family had a past history of pertussis infection.

There were two other examples of delay in onset of symptoms. One father developed a cough with day and night paroxysms and whoop from 3 May onwards, although his wife and two children had had paroxysmal coughs by 18 March.

Two sisters had past history of whooping-cough. The elder began coughing about 3 March and the younger on 14 April. They shared the same bed throughout this time. Both had paroxysmal coughs day and night, and the younger vomited, but neither whooped.

These cases must be considered in relation to the accepted incubation period of 7 to 10 days and quarantine period of 28 days from the onset of the illness.

Treatment

All four doctors concerned and a considerable number of the patients were most impressed by the efficiency of atropine methonitrate (Eumydrin) in the recommended dosage in controlling the number and severity of the paroxysms. This was most noticeable if the family's supply of the drug ran out. In one case in particular treatment was discontinued because a boy of 10 was thought to have recovered at the end of six weeks, having coughed very little for a week. He had no atropine methonitrate for one day, and that night had hourly spasms with recurrence of his whoop, and on four occasions the spasms ended in vomiting. He was started on the drug again at 10.15 the next morning and had one paroxysm of coughing, ending in vomiting, just before his second dose four hours later. Thereafter he had no further vomiting and his cough was minimal. He slept soundly through the whole of the following night.

Although the *Bord. pertussis* was reported by the laboratory to be sensitive to tetracycline, the clinical impression was that tetracycline, even if given very early, had little effect on the progress of the illness. It was used more often with the younger children (see Table II). Its effect in limiting complications cannot be estimated. All the other bacterial pathogens isolated were sensitive to tetracycline. Amylobarbitone and butobarbitone were also used in some cases to reduce the frequency of nocturnal paroxysms.

Discussion

An attempt was made to study an epidemic of whooping-cough in a well-contained community by regular and personal observation of all the families at risk. We were very conscious of the limitations of our study, and made no attempt to assess the severity of the illness by counting paroxysms, especially as the treatment which we agreed upon would be likely to influence this.

The difficulty of early diagnosis was forcibly shown. The large number of children who initially had coughs but were not seen by their doctor is noteworthy, and this contributed greatly to the scale of the epidemic. In early cases diagnosis is impossible and can only be suspected. The presence of a whoop was noted in only 20% of cases of paroxysmal cough (Table II). We were unable to assess whether this low percentage of whooping was due to lack of virulence of the particular strain of the organism, to the modifying effect of immunization, to the effectiveness of our treatment, or to the completeness of our coverage of coughs in the community affected. Vomiting after cough appeared more often, haemorrhagic manifestations were rare, and the most constant finding was a paroxysmal cough by day and/or night of over two weeks' duration. In the presence of other cases of a similar kind diagnosis could be presumptive.

The full clinical syndrome of paroxysmal cough, vomiting, and whoop has been accepted as diagnostic of pertussis infection, but it is now claimed that adenoviruses and other virus infections can cause a similar illness. In this epidemic *Bord. pertussis* was grown. Ramsay (1961) claims that a positive culture can be obtained in 80–90% of cases, and the M.R.C. Report (1951) gave 60% bacteriological confirmation. However, Lautrop and Lacey (1960) state that the isolation of pertussis requires specialized laboratories, using freshly prepared culture media and specially trained personnel. They describe Lacey's procedure as being a method of overcoming these difficulties, but it was not used in our study. In view of their comment on the use of freshly prepared media it is interesting to note the isolation of seven positive cultures within two days at the beginning of our bacteriological studies. We are informed that our laboratory prepared fresh culture media every two to three days.

The request for pertussis culture is very rare in the London Public Health Laboratory Service (J. R. Davies, personal communication, 1964). From our own experience we would presume that this is due to the lack of successful isolation. The Public Health Laboratory in Manchester has about 20% isolation from cases thought to be whooping-cough in general practice, though it has a higher rate from second cases in a family. This laboratory supplies culture plates for inoculation

at the bedside (J. O'H. Tobin, personal communication, 1964). Our isolation rate of 14% must be considered in relation to these reports.

Spread of infection throughout the community was wide and uncontrolled. Out of 408 persons studied, taking a paroxysmal cough as a diagnostic criterion, 30% contracted the infection (Table II). One-fifth of these gave a definite history of previous pertussis infection and yet developed the disease again. The age incidence of pertussis follows the pattern of immunizing infections of childhood, and although second attacks do occur they are very much rarer than would be expected if infection did not confer immunity (Miller *et al.*, 1960). In conflict with this general experience our results show no protection from prior infection. Two explanations may be considered. First, immunity waned rapidly, possibly because of the lack of booster infections in a relatively isolated community. This possibility is supported by the observation that a large number of those suffering second attacks were over 15 years old. Second, the outbreak of infection which we observed might have been due to a different type of aetiological agent.

We were particularly disturbed by the ineffectiveness of the vaccine in this very well immunized community, which is illustrated in Tables III and IV. The schoolchildren aged 5 to 8 had had a booster dose at school entry, but they had an attack rate of over 50%. In the immunized pre-school children the attack rate was 22%. There was little evidence, if any, of protection, yet on the basis of the M.R.C. Report (1951) substantial protection should have been conferred by the vaccine. It seems unlikely that the quality of the vaccine can have changed since the time of the M.R.C. report, as this is controlled by the mouse-protection test established by the M.R.C. studies (1956). It might be that in the community we studied the immunity conferred by the vaccine was overcome by a heavy recurrent infecting dose. Alternatively, the infecting organism might be antigenically different from those incorporated in the vaccine. The disease which we observed was whooping-cough from a clinical viewpoint, and in our opinion there can be no doubt, on the basis of the bacteriological findings, that it was due to *Bord. pertussis*. The organism isolated from this epidemic was found to contain only type 1,3 agglutinogen, and we are informed that until November 1963 the vaccine we used contained only type 1,2,4 strains (A. J. Beale, personal communication, 1964). Preston (1963) has suggested that vaccines lacking type 3 agglutinogen might fail to immunize against prevalent type 1,3 strains. The failure of protection from both previous infection and immunization is readily explainable if in fact type 1,2,4 strains fail to immunize against type 1,3 strains. Our results therefore provide support from the field for Preston's opinion.

The severity of the disease should be correlated with the effect of immunization. Our survey did not attempt to assess severity, but our impression was that the illness was a mild one. We are unable to estimate whether this mildness was due to the particular strain of organism or to the effect of immunization or treatment. Complications were not a feature of the disease studied, but the protracted discomfort, loss of sleep, and domestic disruption were considerable, particularly when one case followed another in a household. Only two patients could be described as seriously ill from this outbreak. There were no deaths, and no patient needed hospital admission. A paediatric domiciliary consultation from a distance of 30 miles (48 km.) was required for one baby, 10 weeks old, who subsequently progressed satisfactorily. One child of 6 years had a haemoptysis, and was found to have a bronchopneumonia, confirmed by *x*-ray examination.

The quarantine regulations were relaxed by the M.O.H. because of the high immunization rate. This spread of the infection among the immunized children and by them was unexpected. Quarantine is therefore still necessary. The role of the school as the disseminator of infection stands out clearly. The teachers were in no doubt of the inadvisability of relaxing the quarantine restrictions. Two of the three teachers and one school cleaner became infected, and teaching was also made very difficult by the coughing of the pupils. The repeated and concentrated exposure to infection in the school may have been responsible for overwhelming the acquired immunity, or it may be, as we have suggested, that the antigenic differences between the strain causing the outbreak and the strains in the vaccine were responsible for the breakdown of protection. The advantage that might have been obtained by a reinforcing injection at the beginning of the epidemic would have to be weighed against the possible chances of neurological complications.

Conclusions

The immunization given against pertussis was ineffective in preventing the spread of an epidemic.

Fully immunized schoolchildren under 8 years of age were not protected from infection, but there was a reduced incidence of paroxysmal coughs in fully immunized pre-school children.

Our observations give some support for the theory that lack of type 3 agglutinogen in a pertussis vaccine may produce inadequate immunization against type 1,3 strains.

Claims of an 80–90% positive-culture rate for pertussis seem unduly optimistic. In general practice bacteriological culture of pertussis is more likely to be of value in confirming the nature of an epidemic than in diagnosing the individual case.

Whooping, which occurred in only 20% of cases with paroxysmal coughs, was of confirmatory rather than diagnostic value.

A previous attack of whooping-cough gave no adequate protection in this epidemic.

Quarantine is still a necessary measure in the control of whooping-cough.

Summary

An epidemic of whooping-cough was traced through a village school and from it to the families of the schoolchildren. The results of previous protective immunization proved very disappointing. Quarantine regulations were suspended because of the large number of children previously immunized, and this is believed to have contributed to the spread of infection. Bacteriological culture of pertussis was of value only in confirming the nature of the epidemic. With immunization, and treatment with atropine methonitrate (Eumydrin) and antibiotics, this proved to be an unpleasant rather than a dangerous illness. Our present clinical criteria and laboratory methods are quite inadequate for diagnostic purposes.

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