BRITISH MEDICAL JOURNAL

LONDON SATURDAY AUGUST 18 1945

TRIAL OF WHOOPING-COUGH VACCINE IN CITY AND RESIDENTIAL NURSERY GROUPS

A REPORT TO THE MEDICAL RESEARCH COUNCIL

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During the years 1942 to 1944 an attempt was made to assess the prophylactic value of a pertussis vaccine by comparing the fate of inoculated children with that of control children. In Oxford City the trial was run in conjunction with the Public Health Department; it comprised 327 inoculated and 305 control children, who were followed up for over a year after their last inoculation. During this time only sporadic cases of whooping-cough occurred. From Nov., 1942, onwards small but similar groups of inoculated and control children were observed in eight residential nurseries for evacuees. In four of these nurseries (Nos. 1, 2, 5, and 8) an epidemic of whooping-cough occurred some time after the inoculations were completed, enabling the experience of the two groups to be compared. The outbreak at one of these nurseries (No. 1) has already been reported (McFarlan and Topley, 1943), but for the sake of completeness it is included with three other outbreaks at Nurseries 2, 5, and 8, to be described now. The present report summarizes the evidence obtained using a total (English) dosage of 40,000 million organisms in Oxford City and two residential nurseries (Nos. 1 and 2), and a higher dosage at two other residential nurseries (Nos. 5 and 8). The investigation was carried out under the direction of the Whooping-cough Subcommittee of the Infectious Diseases Committee of the Medical Research Council.

The vaccine was prepared by Messrs. Burroughs Wellcome and Co. For the vaccine used in Oxford City and residential Nurseries 1 and 2 a mixture of three strains of *H. pertussis* in Phase I was employed, each of which had been grown for 3 days at 37° C. on a Bordet-Gengou medium containing 33% of horse blood. The growth was suspended in 0.5% phenolized distilled water, the function of the water being to lyse the horse-blood corpuscles in the vaccine. The suspension was filtered through muslin and allowed to stand for 7 days at 4° C. The haemolysed supernatant fluid was then discarded and the deposit washed once in 0.5% phenolized saline. The vaccine was suspended finally in 0.5% phenolized saline and standardized by Brown's opacity tubes to a calculated strength of 20,000 million organisms per ml. No heat was applied to the vaccine at any stage of the preparation; the organisms were both killed and preserved with 0.5% phenol. In the vaccine used at residential Nurseries 5 and 8 the organisms were killed and preserved with 1:10,000 merthiolate; in all other respects the preparation of the vaccine was the same as for the earlier batches.

It is important to point out that the methods used for the standardization of vaccines in this country and the United States yield grossly discrepant results. The reason for this need not be discussed here. It is sufficient to draw attention to the difference, which is clearly of importance in assessing the results of comparative trials in the two countries. Observations made at the Wellcome Physiological Research Laboratories (for an account of which we are indebted to Dr. H. J. Parish) showed that the Wellcome vaccine, stated on the label to contain a given number of organisms, was about four times as turbid as that of a Parke Davis vaccine from Detroit having the same labelled strength. Prof. G. S. Wilson (personal communication), who, in this laboratory, compared a number of batches of the Wellcome vaccine with batches of the Parke Davis vaccine, using both turbidity estimations and direct enumeration of the organisms in a Helber chamber under dark-ground illumination, found that by both methods the Wellcome vaccine was over three times as strong as the Parke Davis vaccine.

TABLE I.—*Methods of Inoculation and Time Relation to Whooping-cough Cases*

Place of Trial	Method of Killing and Preserving the Vaccine	Volume given at Inoculation (Inoculation Number) 1	2	3	4	Time Interval between Inoculations	Total Dosage in Millions of Organisms*	Date of Last Inoculation	Time of Onset of First and Last Cases of Pertussis	Time Interval: Last Inoculation to Onset of First Case in Epidemic
Oxford	Phenol	1 ml.	1 ml.	0	0	4 weeks	40,000	Jan.–March, 1943	Cases observed Mar., 1943, to July, 1944	No epidemic
Nursery 1	,,	1 ml.	1 ml.	0	0	,,	40,000	Dec. 21, 1942	April 4, 1943, to end of May	4 months
,, 2	,,	1 ml.	1 ml.	0	0	,,	40,000	Jan. 1, 1943	Oct. 16, 1943, to end of Nov.	9 ,,
,, 5	Merthiolate	1 ml.	1 ml.	1 ml.	2 ml.	1 week between 1st, 2nd, and 3rd; 4 weeks between 3rd and 4th	100,000	Dec. 30, 1943	April 22, 1944, to middle of July	4 ,,
,, 8	,,	0·5 ml.	0·75 ml.	1 ml.	0·75 ml.		60,000	March 15, 1944	March 28, 1944, to June 6	2 weeks

* As pointed out in the text, the figures given in this column would have been about three times as large if the vaccine had been standardized in the United States.

The vaccine was injected intramuscularly into one or other arm. If A.P.T. was given at the same time it was injected at another site. The volumes inoculated and the time intervals between the inoculations are shown in Table I. The

total dosage of about 40,000 to 100,000 million organisms would probably correspond to an American dosage of about 120,000 to 300,000 million.

Although the time interval between the last inoculation and the first exposure of the children to whooping-cough ranged from 2 weeks to 9 months, and although in Oxford City 1 to 6 children in the investigation developed whooping-cough every month up to 18 months after the last inoculation, the number of cases was too small to justify any attempt at correlation between this interval and the incidence of whooping-cough among the two groups. It was not possible to obtain sera from the children for either complement-fixation or agglutination tests.

Reactions to the Pertussis Vaccine.—No severe reactions occurred in the children in Oxford City and residential Nurseries 1, 2, 3, and 4, where a total dosage of 40,000 million organisms was given. It was found impracticable in Oxford itself to get reliable information from the homes, but at each nursery a careful record was kept. At Nursery 1, for example, 10 out of the 12 children inoculated were reported to have had local reactions after their first but not after their second inoculation; only one was at all marked. There were no general reactions. On the other hand, the experience at Nurseries 5, 6, and 7, where another batch of vaccine was given in a total dosage of 100,000 million organisms, was disturbing. The general reactions were so severe as to condemn the further use of the vaccine in this dosage. Each of the 17 children inoculated developed a febrile reaction after the first inoculation. In two children the highest temperature recorded was 104° F. and 104.8° F. respectively, and the pyrexia lasted 7 to 10 days. The remaining children had temperatures of 99.4 to 101° F., which returned to normal in from 1 to 3 days. Pyrexial reactions (99 to 102° F.) followed each subsequent inoculation in all but one of the 14 children who received the full course. At the site of the inoculation the area of redness never exceeded 3 in. in diameter, and was generally less than this; but the local reactions did appear to disturb the children. For this reason when Nursery 8 was visited the dosage of vaccine inoculated was reduced to 60,000 millions; the reactions, however, both general and local, were enough to make the widespread use of this dosage undesirable.

The methods of selection of the inoculated and control groups, the evidence of their similarity, and the experiences of these groups are perhaps best described separately for Oxford City and for the residential nurseries.

The Oxford City Trial

The two series of children were chosen from those who were more than 6 months and less than 3 years of age on Jan. 1, 1943, who normally attended the infant welfare clinics or wartime day nurseries of the Public Health Department, and who had no history of whooping-cough or of inoculation against it. The majority of children had their consent forms signed and the first inoculation given at the same time as a normal visit to the clinic, and often at the same session as an A.P.T. inoculation against diphtheria. The propaganda was carried out not only at the clinics but also by the health visitors, who during their routine home visits persuaded the mothers to bring their children up to the clinics for whooping-cough inoculations. It therefore needed very little effort on the mother's part to have her child inoculated. The control children were chosen from the clinic record cards, which at each clinic were filed in order of the date of first attendance. For every child inoculated, a card was picked at random from the cluster of cards about the same place in the file as that of the inoculated child. The first card picked of a child of the same sex, approximately the same age, and with no history of whooping-cough or inoculation against it, was marked "Whooping-cough Investigation" and the child's name was included in the control group. The inclusion of a child in this group was not determined in any way by the circumstance that its mother had refused permission for inoculation.

The children attending wartime day nurseries were chosen separately. Those eligible in each nursery were divided according to age and sex into inoculated and control groups, using the same methods as described for the residential nurseries. When a child left Oxford or was inoculated against whooping-cough by a general practitioner it was excluded from the investigation. At the end of the period of observation there were 305 control and 327 inoculated children in the series. The nursery population had altered greatly.

Evidence of Similarity.—Some of the characteristics that might affect the incidence of whooping-cough were recorded in the two groups. χ^2 and χ_c tests (Fisher and Yates, 1943) were applied to the data to determine how far the differences in incidence might be considered to be the result of sampling variation. The differences in distribution of (1) number of children in family, (2) number of other susceptible children in family, (3) number attending day nurseries or nursery classes, (4) number suffering from measles before or during the investigation, were in no instance greater than could be accounted for readily by sampling variation. However, the frequency of prior inoculation with A.P.T. was significantly less ($P < 0.005$) in the control group than in the inoculated group (49% in the control group and 73% in the inoculated group had at the beginning of the experiment a history of A.P.T. inoculation). Fifty-one per cent. of the children in the control group and 89% of the children in the inoculated group, who had not received A.P.T. at the beginning, received it in the course of the investigation. Thus the frequency with which inoculated children were brought for A.P.T. remained consistently higher than that in the control group.

Since this difference between the two groups might have a bearing, as an index of maternal care, on the incidence of exposure to pertussis, the effect on pertussis incidence has been carefully investigated. There is a difficulty, in that all but 6 of the 89 inoculated children who had not received A.P.T. at the start of the investigation had received it at the end. In the control group 154 (50%) had not received A.P.T. at the beginning of the investigation, and 76 (25%) had still not received it at the end. Thus it is unlikely that any A.P.T. effect could be established in the inoculated group, and, in fact, the differences in incidence are well within sampling variation. In the control group, in which an A.P.T. effect might have been observed, there is an even smaller difference in relative frequency of the incidence of pertussis. No evidence was obtained that the A.P.T. distribution was relevant to the experiment.

So far as it is possible to judge, it appears that the two series of inoculated and control children were fair random samples of the susceptible Oxford clinic children between 6 months and 3 years of age.

Follow-up Observations.—These children were observed for 12 to 18 months, starting Jan. to March, 1943, and ending March to July, 1944. Observation of the inoculated children was begun 3 to 28 days after their last inoculation. The control children were selected and visited during the inoculation period, and their beginning of observation was made to correspond with that of the inoculated children. The date of the last observation was the date of the last visit to the home. A chart was compiled to show the number of inoculated and control children, and the number of cases of whooping-cough among them, for every month from Jan., 1943, to July, 1944. In no month was there any significant difference in the proportion of inoculated and control children. It follows that the average length of observation per child was the same in the two groups. Owing to shortage of staff it proved impossible to pay regular visits to the home of each vaccinated and control child in the series. Cases or contacts were visited by one of us (A. M. M. and later E. T.) as soon as possible after they were notified to the Public Health Department by the medical practitioners or by the health visitors. The notifications were necessarily often made late in the disease or even weeks later. In only 28 instances was it considered worth while taking a nasopharyngeal swab from a child in the investigation or from a member of its family who had definite whooping-cough. In only six of these cases was *H. pertussis* isolated. During the spring of 1944 each health visitor reviewed the history of every child on her list who was in the investigation, and in the majority of instances made the final visit herself. However, if there was a history of a suspicious cough or of whooping-cough or of contact with whooping-cough, or a special visit was required for further information, one of us made the final visit. In May, 1944, a list was compiled of every school or nursery that was attended by a child in the investigation and from which one or more cases of whooping-cough had been notified to the

Public Health Department. Each of these was visited once, and the teacher or matron told us which children in the investigation had been in the same class or room as a case of whooping-cough, and whether they had developed pertussis. In a few cases notified for the first time a home visit was made.

The evidence obtained by this method of follow-up is summarized in Tables II and III.

TABLE II.—*Incidence of Whooping-cough among Children exposed to a Case in the Same Room of a Day Nursery or Nursery Class in Oxford City*

	Inoculated Children	Control Children
Number of children exposed	29	25
Number of children developing definite whooping-cough after exposure	5	6
Proportion developing definite whooping-cough after exposure	17%	24%

Statistical analysis of these data shows that there are between 5 and 7 chances out of 10 of obtaining greater differences in the observed frequency of whooping-cough in two similar samples drawn from such a uniform population.

Evidence of Exposure to Whooping-cough.—The monthly record of cases showed no evidence of an epidemic during the investigation. A history of exposure to whooping-cough was obtained more frequently from the mothers of inoculated children than of control children. Thus it appeared from the home-visit data that 27 inoculated and 20 control children had been exposed to whooping-cough in the same house for more than one day. A history of less intimate exposure was obtained from the parents of 36 inoculated and only 14 control children. In the nursery classes of schools and in day nurseries (Table II) there was no significant difference in the frequency of exposure. The evidence from mothers whose children had been inoculated might well be more reliable than that of the mothers of the control children, who did not understand their connexion with the investigation. In the nursery classes and nurseries the same teacher or matron observed a large number of children. The teacher generally knew nothing of the difference between inoculated and control children, whereas the matrons had assisted in the original planning of the experiment and understood clearly the importance of treating them alike. For this reason we should be disposed to pay considerably more attention to the data obtained from the nurseries and schools than from the mothers.

TABLE III.—*Incidence of Whooping-cough, Regardless of History of Exposure, Among All Children in the Investigation*

	Oxford City		Residential Nurseries	
	Inoculated Children	Control Children	Inoculated Children	Control Children
Number of children observed	327	305	33	30
Number of cases of definite whooping-cough	41 (30)*	43 (29)*	18 (15)*	19 (19)*
Number of cases of doubtful whooping-cough	10	6	5	3
Proportion of children with definite whooping-cough	12·5%	14·1%	54·6%	63·3%

* The figures in brackets represent the numbers of definite cases of whooping-cough which both whooped and vomited.

Statistical analysis shows that the probabilities of obtaining more widely different frequencies in two samples from the same population are 0.5–0.7 for the Oxford City samples and 0.3–0.5 for the residential nursery samples.

Evidence of Incidence of Whooping-cough.—This evidence is clinical, not bacteriological. Its only claim to uniformity is that the diagnosis was decided by home visits made by the same person, who used the same method of approach to inoculated and control children. The original notifications were, as stated above, made by general practitioners and health visitors. Each health visitor had approximately equal numbers of inoculated and control children on her lists, and appreciated the importance of treating them alike. It can be seen from Table III that the frequency of clinically definite cases of whooping-cough was similar in the inoculated and control groups of children. It is more difficult to assess accurately the incidence of whooping-cough among children with a history of exposure to the disease. We have reason (see above) to doubt whether the mothers of inoculated children gave reports comparable with those from mothers of the controls. For this reason Table II presents the evidence for the incidence of cases among children exposed in nursery classes or day nurseries only. The differences in incidence of whooping-cough—first, between all the inoculated and all the control children, and, secondly, between the small numbers of inoculated and control children known to be exposed to whooping-cough in day nurseries or nursery classes—can be accounted for entirely on the basis of sampling variation.

Although in each case a note was made of the maximum number of whoops per day and the presence or absence of vomiting, the results depended on the, often distant, memory of a wide variety of mothers and cannot be regarded as reliable. Most cases were mild. Only four were complicated by pneumonia—two in inoculated and two in control children.

The Residential Nurseries

The methods of selecting the inoculated and the control groups, the evidence for their similarity, and the experience of these groups will be discussed for all four nurseries together. These nurseries, all in the home counties, are housed in mansions used temporarily for the care of evacuee children. Each is an isolated community cared for by a residential staff, sometimes aided by daily helpers.

In each nursery every child from 6 months to 3 years of age who had no history of whooping-cough or of inoculation against it was included in the trial. At Nurseries 5 and 8 the upper age limit was raised to 4 years in an attempt to get larger groups of children. The eligible children were divided into two groups of almost equal age and sex distribution. In Nurseries 5 and 8 it also proved necessary to ensure an even distribution of the two groups in the same room or unit—in Nursery 5 because of a suspected case of whooping-cough at the time of the first inoculation, and in Nursery 8 because of the greater degree of segregation. If the mother of a child selected for inoculation refused to give her consent the child was placed in the control group and a corresponding "control" child selected for inoculation instead. In each residential nursery the two groups of children were similar in every respect except inoculation. For months or years they were cared for and fed by the same staff and exposed to the same risks of infection.

When whooping-cough was reported in a residential nursery it was visited at once, and thereafter at weekly to monthly intervals throughout the epidemic.

The evidence of equal and definite exposure to whooping cough was very much more reliable than is possible among children living at home. In each outbreak *H. pertussis* was isolated from at least one child with clinical whooping-cough. At every visit the matron told us of the dates that any child had been moved from one room to another. It was clear that in each of the four nurseries all the selected children had been exposed to a whooping-cough case that had lived and slept in the same room while in the catarrhal and paroxysmal stages of the disease.

The evidence for the occurrence of whooping-cough was also more reliable than is possible among children living at home. The children were observed throughout by the same staff and by the matron, who, each time we visited the nursery, gave us the clinical details which she had collected for all the children in the investigation. The findings are summarized in Table III. The cases were nearly all mild. Two cases in Nursery 8 and one case in Nursery 2 were considered more severe by the matrons. These were control children. The evidence obtained on the maximum number of whoops per day was necessarily less reliable and showed nothing significant. Only one child showed marked loss of weight during the illness. This was a control child who developed a dubious pneumonia. No other complications occurred.

These facts, together with the data in Table III, emphasize the smallness of the figures on which any conclusion from the nursery material must be based. All that can be said is that the difference in the incidence of whooping-cough in the inoculated and control groups can be accounted for entirely on the basis of sampling variation. No satisfactory evidence was obtained that the vaccine was of any value in modifying the course of the disease.

Discussion

The Oxford City evidence has the advantages and disadvantages of a city field trial. These have already been discussed. The results show that the pertussis vaccine in a total (English) dosage of at least 40,000 million organisms did not significantly affect the incidence of whooping-cough. In the residential nursery trials the groups were almost identical in constitution and risk of exposure to infection, and the clinical data were more reliable, but the number of children under observation was necessarily much smaller. The results, however, bear out the findings in Oxford City that the vaccine was of no value in preventing whooping-cough.

Doull and his colleagues (1939) have already recorded results almost as disappointing as our own; but the majority of the reports from the United States and Canada suggest that vaccination against pertussis is effective. Although it is possible to find faults with points in the planning or statistical analysis of some of the trials it is difficult to avoid the conclusion that vaccination conferred some protection. It is noteworthy that most of these trials were carried out in clinic populations in which it is extremely difficult to obtain perfect equalization of the inoculated and control groups, particularly in regard to exposure to infection. In one of the few trials conducted in residential institutions, where a far greater degree of similarity can be attained between the two groups, little or no success was claimed (Siegel and Goldberger, 1937).

Our own results may be criticized on the ground that the vaccine was of insufficient antigenic potency or that the dosage employed was too low. Examination of the data recorded by different observers who have apparently been successful in whooping-cough prophylaxis shows that a wide variety of vaccines has been used, and there is little to suggest that any one method of vaccine preparation is greatly superior to any other. In respect of dosage, we have already pointed out that there is a gross discrepancy between the results yielded by the methods of vaccine standardization in this country and the United States, and that if our vaccine had been prepared in an American laboratory its strength would have been estimated at about 60,000 millions instead of 20,000 millions per ml. It is probable, therefore, that our total dosage was higher than that used in any of the investigations recorded in Canada or the United States. This is borne out by the severity of the reactions that we obtained after inoculation of the larger doses of vaccine.

Since the possibility could not be excluded that the Wellcome vaccine used in our investigations differed in some material way from vaccines prepared in the United States and Canada, it was decided by the Whooping-cough Subcommittee of the Preventive Medicine Committee of the Medical Research Council to carry out a fresh investigation in which a vaccine of American origin was used. Such a trial is now being undertaken in Oxford, under carefully controlled conditions, using a vaccine manufactured by Messrs. Parke Davis of Detroit to the formula of Dr. Sauer, of Evanston, Ill. The results of this inquiry will, it is hoped, be published in due course.

Summary and Conclusions

Over 600 susceptible children of 6 months to 3 years of age attending welfare clinics and wartime day nurseries in Oxford City, and 110 evacuee children of 6 months to 3 or 4 years of age distributed in eight residential nurseries in Oxfordshire, Berkshire, and Buckinghamshire, were divided into "inoculated" and "control" groups by methods designed to render the two groups similar in every respect other than inoculation.

The inoculated children were given either two doses of pertussis vaccine at a 4-weeks interval, or four doses at intervals of 1, 1, and 4 weeks. The total dosage ranged from 40,000 to 100,000 million organisms, corresponding to an American dosage of about 120,000 to 300,000 millions.

Whooping-cough occurred sporadically in Oxford City during the succeeding 18 months, and broke out in four of the residential nurseries 2 weeks to 9 months after the last inoculation.

No significant difference was observed in the incidence or severity of whooping-cough between the inoculated and the control children. In Oxford City 12.5% of 327 inoculated and 14.1% of 305 control children developed definite whooping-cough. In the residential nurseries the corresponding figures were 55% of 33 inoculated and 63% of 30 control children.

The evidence obtained from this investigation lends no support to the view that pertussis vaccine is of value in the prophylaxis of whooping-cough; and it is suggested that the use of this vaccine should be discontinued till some positive evidence of its value is obtained in further carefully controlled trials.

We are indebted to Dr. R. B. Fisher for statistical advice; to Dr. G. C. Williams, Medical Officer of Health, Oxford C.B., for permission to carry out the investigation among the children under his care; to the medical officers and health visitors on his staff for their co-operation and active help; to Dr. E. Donaldson, Principal Regional Medical Officer, for his assistance in the choice of suitable residential nurseries; to the Waifs and Strays Society, the Margaret Club Day Nursery, the Whitefield Day Nursery, and the county councils of Buckinghamshire, Berkshire, London, and Oxfordshire, for permitting us to visit these nurseries; to the medical and nursery staff of each nursery we selected, particularly to Dr. J. A. Hill, Dr. G. N. Stathers, Dr. G. R. N. Henry, and Dr. N. Black; and to the Matrons of Cottesford House, Culham Court, Waddesdon Manor, and the Margaret Club Day Nursery for the collection of much of the data we needed. We particularly wish to thank Messrs Burroughs Wellcome and Co. for the free supply of vaccine.

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PROBLEMS OF NAVAL WARFARE UNDER CLIMATIC EXTREMES*

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PART III.—LECTURE II (*continued*)

Psychological Effects of Long Service in the Tropics

A common opinion in the Tropics is that after about a year there is a noticeable deterioration in drive, alertness, keenness, memory, the capacity and speed of thought, and power of making decisions. These symptoms may be accompanied by an obvious lassitude, procrastination, irritability, sometimes bibulousness, and slovenliness in personal appearance. The better-educated are conscious of their own declining efficiency, and they note the same change in others; that is to say, the phenomena are both subjective and objective. The symptoms are popularly ascribed to the climate, whether hot and humid or hot and dry, and the point of view is freely ventilated that one to two years should be the maximum tenure in uncongenial tropical regions.

Since we are waging a naval campaign in equatorial waters, the problem has many important bearings. Medical advice is needed on several points. Do, in fact, changes in intellect or personality follow long tropical residence? If so, what is their nature?; how can they be prevented or alleviated?; what is the optimum duration of tour in the Tropics?

A new-comer may be struck by certain personality traits in some who have served for a time on a tropical station—traits made up of undue irritability, alcoholic indulgence, mild hypochondriacal preoccupation, and a tendency towards paranoid feelings of resentment. Castellani applied the term "cacophoria tropicalis" to a state of lassitude and mild general malaise. Whether actual falling off in performance and intellectual capacity exists we do not know for certain, but we suspect it. To determine the nature of this clinical picture is important. Superficially, the syndrome might strike one as representing a mild dementia with some personality deterioration were it not for the victim's clear insight and the fact that the condition is apparently "cured" after leave at home. More probably it belongs to the realm of the neuroses, with hysterical features motivated by a strong if thinly veiled desire to return home: in other words, a nostalgic reaction.

* Being the Croonian Lectures delivered to the Royal College of Physicians, July 10 and 12, 1945.