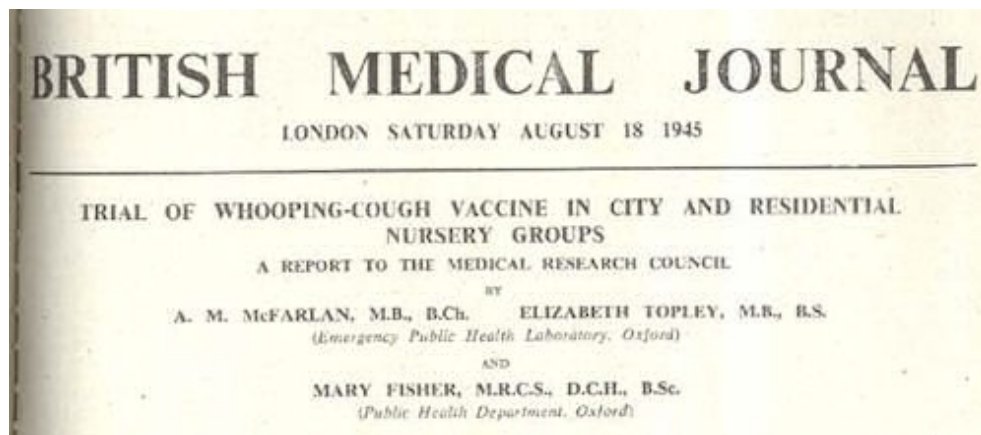


[Download key passages/title pages as a PDF](#)

McFarlan AM, Topley E, Fisher M (1945). Trial of whooping-cough vaccine in city and residential nursery groups. *BMJ* 2:205-208.

Key passages



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

ing 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

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

nursery material must be used. 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.

[Home](#)[Contents](#)