Papers and Originals

Vaccination Against Measles: Clinical Trial of Live Measles Vaccine Given Alone and Live Vaccine Preceded by Killed Vaccine

Second Report to the Medical Research Council by the Measles Vaccines Committee*

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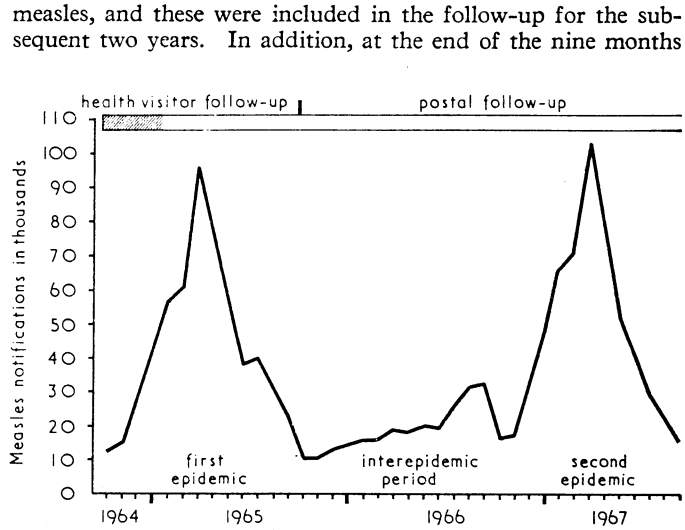
In the autumn of 1964 a large-scale trial of measles vaccines was begun in Britain under the auspices of the Medical Research Council's Measles Vaccines Committee. The trial was planned to assess the value of the vaccines for general use, and special attention was therefore paid to the degree and frequency of reactions occurring after vaccination and the ability of the vaccines to protect against measles.

A preliminary report of this trial covering the six months after vaccination has already been published (Medical Research Council, 1966) and gives details of its general plan. The trial was arranged in 32 areas and more than 36,000 children, in the susceptible age group of 10 months to 2 years, took part. Two immunization procedures were investigated—a single dose of killed vaccine followed one month later by live vaccine, and live vaccine alone. The killed vaccine was prepared by Pfizer Limited from the Enders–Edmonston B strain, and the live vaccine by Glaxo Laboratories Limited from the Schwarz strain. The children were allocated by an effectively random process to the three groups: (*a*) killed/live vaccine (*b*) live vaccine, and (*c*) no vaccine. The three groups were shown to be similar in various characteristics relevant to the risk of exposure to measles. The children were followed up by health visitors at three weeks to assess reactions to vaccination and at three, six, and nine months to record the incidence of measles; additional information on the cases was obtained from the general practitioners.

The results showed that reactions to both schedules of vaccination were generally mild. They also showed that each schedule induced about 85% protection against measles for six months and, furthermore, those vaccinated children who contracted measles had on average a milder attack than those who had the disease in the unvaccinated group.

The findings on the protective effect of the vaccines were based on an analysis of the results of all the children, whereas those on similarity of groups and on reactions to vaccination were from an 11% sample and have since been confirmed by a full analysis for all the children (not reported here).

The trial has now been in progress for two years nine months after vaccination covering the two epidemics of 1964–5 and 1966–7. The results on protection during the whole of these periods have been analysed and are reported here. The analysis has been made in two separate parts—namely, for the first nine months after vaccination (which includes the six months already reported on) and for the subsequent two years (see Chart). There were a number of reasons why this separate analysis was essential. At the end of the nine months, in accordance with a promise made when the trial was initially arranged, measles vaccine was offered to all the unvaccinated children. This offer was accepted for many of the children, who were accordingly excluded from the trial. There still remained, however, a large number of unvaccinated children who had not had measles, and these were included in the follow-up for the subsequent two years. In addition, at the end of the nine months



Statutory notifications of measles in England and Wales in four-week periods from September 1964 to August 1967. The horizontal block indicates the period of this trial and the shaded area the period during which the vaccines were given.

* This study was made under the auspices of the Measles Vaccines Committee of the Medical Research Council in collaboration with the Medical Officers of Health in a number of areas in Britain.

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A number of medical officers of health in other areas helped with the follow-up.

All field work was carried out by the medical, nursing, and clerical staff of the medical officers of health.

The trial was co-ordinated by: Dr. C. L. Miller, N.I.M.R. (Hampstead Laboratories), London N.W.3, and Dr. T. M. Pollock, Central Public Health Laboratory, Colindale, London N.W.9.

The clerical work of the trial was co-ordinated by: Mrs. A. Allchin, N.I.M.R. (Hampstead Laboratories), London N.W.3.

The analyses of the results were made by: Mr. J. Pope, Central Public Health Laboratory, Colindale, London N.W.9.

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five of the areas which had taken part in the trial (Bristol, Cardiff, Hull, Oxford, and Southampton) agreed to begin a new investigation of community vaccination against measles and were therefore excluded from further follow-up. Furthermore, after the first nine months the health visitor follow-up was replaced by postal inquiries.

Results of Follow-up During First Nine Months

A total of 36,211 children took part in the trial for the first nine months—10,434 in the killed/live vaccine group, 9,538 in the live vaccine group, and 16,239 in the unvaccinated control group. (These figures differ slightly from those in the previous report (Medical Research Council, 1966), which were provisional.) The proportions followed up by health visitors in the three groups respectively were 90%, 87%, and 84%.

Protective Effect of Vaccination

Table I shows the cases of measles reported by the parent to the health visitor and the proportions seen and diagnosed as measles by the doctor. Of the reported cases the doctor saw and confirmed 48% in the killed/live vaccine group, 47% in the live vaccine group, and 66% in the control group. The difference in the proportion of confirmed cases between the vaccinated and control groups may have been because many of the cases of measles reported by the health visitor as having occurred in vaccinated children were of a mild and transient nature as a result of immunization (see Table II).

TABLE I.—*Cases of Measles During First Nine Months*

Group	No. of Children	No. of Cases of Measles Reported by Parent through Health Visitor	No. of these Cases Seen by Doctor and Diagnosed as Measles*		Rate: Confirmed Cases per 1,000	Percentage Protection
			No.	%		
Killed/live vaccine ..	10,434	443	211	48	20	85
Live vaccine	9,538	434	202	47	21	84
Unvaccinated control ..	16,239	3,286	2,169	66	134	—

* Including a few cases where the doctor was doubtful of the diagnosis (see Table II).

TABLE II.—*Doctor's Assessment of Severity of Measles During First Nine Months*

Group	No. of Cases*	Doctor's Assessment							
		Doubtful Measles		Mild		Moderate		Severe	
		No.	%	No.	%	No.	%	No.	%
Killed/live vaccine ..	201	27	13	133	66	37	18	4	2
Live vaccine	195	12	6	137	70	42	22	4	2
Unvaccinated control ..	2,011	18	1	938	47	969	48	86	4

* Excluding those cases with no assessment of severity.

The results in Table I show that both schedules induced substantial and similar protection. On the basis of the confirmed cases the degree of protection for the killed/live vaccine group was 85% and for the live vaccine group 84%. A similar degree of protection, though not quite so great, was also obtained when calculated from the total number of cases reported by the parent; 79% for the killed/live vaccine group and 77% for the live vaccine group.

Modification of the Disease by Vaccination

When measles occurred in vaccinated children it was on average milder than the disease in unvaccinated children (Table II). A small number of specific complications, such as otitis media, pneumonia, and convulsions, were reported by the doctor, but there was no evidence of differences in frequency between the three groups (Table III).

TABLE III.—*Specific Complications of Cases of Measles Reported by Doctor During First Nine Months*

Group	No. of Cases	Specific Complications						Cases Admitted to Hospital	
		Pneumonia		Otitis Media		Convulsions			
		No.	%	No.	%	No.	%	No.	%
Killed/live vaccine ..	211	0	0	6	3	2	1	0	0
Live vaccine	202	0	0	2	1	2	1	0	0
Unvaccinated control ..	2,169	13	1	67	3	12	1	29	1

Follow-up of Ineligible and Defaulter Children

As explained in the previous report, a number of children were excluded from the three main groups either because they were ineligible for vaccination on the grounds of health or because they defaulted from vaccination. These children were also followed up. The incidence of measles in the ineligible and defaulter groups during the first nine months was similar to that in the unvaccinated control group (Table IV). It thus appears unlikely that the necessary exclusion of these children from the three main groups had affected the assessment of the protective effect of the vaccines.

TABLE IV.—*Incidence of Measles Among Those Children Excluded from Main Analysis, During First Nine Months*

Group	No. of Children*	Cases of Measles Confirmed by Doctor	
		No.	Rate/1,000
Ineligible for vaccination ..	4,650	513	110
Defaulter unvaccinated ..	5,352	693	129
Unvaccinated control	16,239	2,169	134

* These figures differ slightly from those in the previous report (Medical Research Council, 1966), which were provisional.

Results of Follow-up During the Subsequent Two Years

As mentioned above, the follow-up during the subsequent two-year period was made on smaller groups of children than those during the first nine months. After excluding the five areas which agreed to study community vaccination and those children in the control group who accepted vaccination after nine months, as well as all the children who were reported as having had measles during the first nine months, there remained a total of 21,653 children—8,171 in the killed/live vaccine group, 7,889 in the live vaccine group, and 5,593 in the unvaccinated group.

Although this unvaccinated group was now no longer a randomly allocated control group, the experience of measles in this group could still be used in comparison with that in the other two groups for assessing the protective value of vaccination. Such a comparison appears to be reliable, since there is evidence that refusal to accept vaccination in this trial either at the beginning (Table IV) or at the end of nine months (Table V) was not associated with the subsequent incidence of measles.

The follow-up during the two years was made by postal inquiry. Questionary forms were sent out on two occasions to all the parents of the children in the three trial groups and also

TABLE V.—*Incidence of Measles Among Those Children Excluded from Main Analysis, During Subsequent Two Years*

Group	No. of Children	Cases of Measles Confirmed by Doctor	
		No.	Rate/1,000
Ineligible for vaccination ..	2,301	530	230
Defaulter unvaccinated ..	3,225	599	186
Unvaccinated (serving as control)	5,593	1,244	222

to the ineligible and defaulter groups. The response to the postal follow-up was good; in each of the two vaccinated groups it was 90% and in the unvaccinated control group 70%. The lower response of the unvaccinated group was probably because it was a less co-operative group, the parents having chosen not to accept vaccination when it was offered at the end of nine months.

Protective Effect of Vaccination

Table VI shows the cases of measles reported by the parent and those seen and diagnosed as measles by the doctor. It is evident, in comparison with Table I, that the proportions of confirmed cases in all three groups were greater, and that the differences between the vaccinated and control groups were less, than those during the nine-months follow-up. This was probably due to an improvement in the arrangements for the rapid confirmation of measles by the doctors. Moreover, those illnesses where the parent was doubtful whether the child had had measles, and the child had not been seen by the doctor, were not included as measles; in the first nine months, however, many such cases were reported as measles by the health visitor and were included among the total cases reported.

TABLE VI.—*Cases of Measles During Subsequent Two Years*

Group	No. of Children	No. of Cases of Measles Reported by Parent through Postal Inquiry	No. of these Cases Seen by Doctor and Diagnosed as Measles*		Rate: Confirmed Cases per 1,000	Percentage Protection
			No.	%		
Killed/live vaccine ..	8,171	308	222	72	27	88
Live vaccine	7,889	162	106	65	13	94
Unvaccinated (serving as control) ..	5,593	1,696	1,244	73	222	—

* Including a few cases where the doctor was doubtful of the diagnosis (see Table VII).

It is seen from Table VI that during the two years both schedules of vaccination continued to induce substantial protection against measles. On the basis of confirmed cases the degree of protection for killed/live vaccine was 88% and for live vaccine alone 94%; the difference between these two figures is significant (at the 0.1% level). A similar significant difference between the protective effect of the two schedules is evident when the degree of protection is calculated from the total number of cases reported by the parents—namely, 87% for the killed/live vaccine and 93% for the live vaccine alone.

A check was made on the occurrence of measles in those children whose parents had not replied to the postal inquiry. A random sample of about 10% of those in each group not answering either inquiry were visited by health visitors. From this sample the number of cases which were seen and confirmed by the doctor were 3 out of 126 visited in the killed/live vaccine group, 1 out of 127 in the live vaccine group, and 37 out of 187 in the unvaccinated group. Though the numbers are relatively small the degrees of protection calculated from the sample, 88% for the killed/live vaccine and 96% for the live vaccine alone, were very similar to those obtained from the main postal inquiry.

With each schedule of vaccination the protective effect may have been even greater than that calculated because the postal follow-up of the unvaccinated group was less complete than that of the two vaccinated groups.

Modification of the Disease by Vaccination

When measles occurred in the vaccinated children it was, as found during the first nine months, generally of a milder form than the disease in unvaccinated children (Table VII). Reports were received of a small number of specific complications which occurred in those cases of measles confirmed by the doctor but there was no evidence of significant differences between the three groups (Table VIII). It is interesting to note, however, that all five cases of convulsions reported were in unvaccinated children. It may also be noted that only one case of encephalitis associated with measles was reported during the whole trial.

TABLE VII.—*Doctor's Assessment of Severity of Measles During Subsequent Two Years*

Group	No. of Cases*	Doctor's Assessment							
		Doubtful Measles		Mild		Moderate		Severe	
		No.	%	No.	%	No.	%	No.	%
Killed/live vaccine ..	209	11	5	152	73	43	21	3	1
Live vaccine	100	3	3	72	72	22	22	3	3
Unvaccinated (serving as control) ..	1,023	7	1	431	42	528	52	57	6

* Excluding those cases with no assessment of severity.

TABLE VIII.—*Specific Complications of Cases of Measles Reported by Doctor During Subsequent Two Years*

Group	No. of Cases	Specific Complications						Cases Admitted to Hospital	
		Pneumonia		Otitis Media		Convulsions			
		No.	%	No.	%	No.	%	No.	%
Killed/live vaccine ..	222	2*	1	8	4	0	0	2†	1
Live vaccine	106	0	0	3	3	0	0	0	0
Unvaccinated (serving as control) ..	1,244	9*	1	44	4	5	0·4	17	1

* Including one case of collapsed lung. † Including one case of encephalitis.

Duration of Protection

A further analysis of the results was made to see whether there was any waning in the degree of protection as the trial progressed. The results for the two-year follow-up were therefore analysed for two separate periods each of a year corresponding to the interepidemic and second epidemic, and compared with those for the first nine months covering the first epidemic (see Chart).

Analysis of All Confirmed Cases

Table IX gives the results of the analysis for these three periods of all the cases of measles confirmed by the doctor. For the three consecutive periods the degrees of protection for the killed/live vaccine group were 85%, 86%, and 89% and for the live vaccine group 84%, 91%, and 95%. It is clear that there was no evidence of waning in the protection produced by either of the vaccination schedules as the trial progressed. It was also shown that the live vaccine alone gave a significantly greater degree of protection than the killed/live vaccine during the second period (at the 2% level) and the third period (at the 0.1% level).

Because the changes in the study populations at the end of the first nine months may have introduced some small bias in the assessments of the degree of protection from vaccination, it would be unwise to interpret the higher percentages during the second and third periods as evidence of an increase in the degree of protection as the trial proceeded.

Analysis of Cases after Home Contact

A more critical assessment of the degree of protection and its duration was made by analysing the incidence of measles in children known to have been exposed to the disease at home. Table X gives the results for the three periods for all the cases of measles reported in children after home contact. For the three consecutive periods the killed/live vaccine gave degrees of protection of 93%, 91%, and 93% and the live vaccine

TABLE IX.—*Duration of Immunity : Confirmed Cases of Measles Occurring During Three Consecutive Periods of Trial*

Group	First Epidemic Period 9 Months				Interepidemic Period 12 Months				Second Epidemic Period 12 Months			
	No. of Children	No. of Confirmed Cases	Rate/ 1,000	% Protection	No. of Children	No. of Confirmed Cases	Rate/ 1,000	% Protection	No. of Children*	No. of Confirmed Cases	Rate/ 1,000	% Protection
Killed/live vaccine ..	10,434	211	20	**85**	8,171	68	8	**86**	8,062	154	19	**89**
Live vaccine	9,538	202	21	**84**	7,889	42	5	**91**	7,837	64	8	**95**
Unvaccinated	16,239	2,169	134	—	5,593	318	57	—	5,187	926	179	—

* Excluding reported cases of measles during previous 12 months.

TABLE X.—*Duration of Immunity : Reported Cases of Measles Occurring in Children in Contact with the Disease at Home During Three Consecutive Periods of Trial*

Group	First Epidemic Period 9 Months				Interepidemic Period 12 Months				Second Epidemic Period 12 Months			
	No.* of Children	Cases of Measles after Home Contact			No.* of Children	Cases of Measles after Home Contact			No.* of Children	Cases of Measles after Home Contact		
		No.	Attack Rate %	Protection %		No.	Attack Rate %	Protection %		No.	Attack Rate %	Protection %
Killed/live vaccine ..	1,075	61	**6**	**93**	483	36	**7**	**91**	1,271	76	**6**	**93**
Live vaccine	1,047	63	**6**	**93**	531	13	**2**	**97**	1,262	25	**2**	**98**
Unvaccinated	1,440	1,177	82	—	209	168	**80**	—	504	411	82	—

* Reported by parent as having been in contact with measles in the home.

alone 93%, 97%, and 98%. It is clear that a high degree of protection against measles from home exposure was induced by both schedules and was well maintained as the trial progressed. Again, it was shown that during each of the second and third periods the live vaccine alone gave a significantly greater degree of protection than the killed/live vaccine (both at the 0.1% level).

As with the analysis of all confirmed cases, it would be unwise to suggest an increase in the degree of protection as the trial proceeded.

It should be pointed out that the smaller numbers of children exposed in the home in the unvaccinated group during the second and third periods compared with those in the vaccinated groups was largely a result of the smaller number of children in the unvaccinated group and the less complete response of the parents to the postal inquiry in this group.

Summary and Conclusions

This report gives the results of a controlled trial which was conducted in a number of areas throughout Britain to assess the value of measles vaccines for general use in children. Two immunization schedules were investigated—a single dose of killed vaccine followed a month later by live vaccine, and live vaccine alone.

Both schedules were found to give a high degree of protection against measles. The results, which cover a total follow-up period of two years nine months, have been analysed for three consecutive periods of nine, twelve, and twelve months, the first and last corresponding to measles epidemics. For these three periods respectively, the degrees of protection based on all confirmed cases were 85%, 86%, and 89% for the killed/live vaccine, and 84%, 91%, and 95% for the live vaccine alone. The corresponding figures based on those children known to have been exposed to measles in the home were 93%, 91%, and 93% for the killed/live vaccine and 93%, 97%, and 98% for the live vaccine alone. The greater protective effect of the live vaccine alone during the two later periods, compared with the killed/live vaccine, was statistically significant. The results also showed that when measles occurred in vaccinated children it was on average milder than the disease in unvaccinated children.

It may be concluded that there is a strong case for the use of live measles vaccine alone. The previous report (Medical Research Council, 1966) showed that the live vaccine alone was generally acceptable with regard to vaccination reactions. The present report has shown that the live vaccine alone gave a substantial degree of protection which was well maintained throughout the whole period of the trial, which included two epidemics. After the first nine months the live vaccine alone also gave a significantly higher degree of protection than the killed/live vaccine. Further, the use of live vaccine alone has the advantage that only one injection is required. It is desirable, however, that parents should be informed that live vaccine alone sometimes induces a febrile disturbance or a mild measles-like illness which is non-infectious, so as to avoid undue concern if such reactions should occur.

It may be argued that an injection of killed vaccine is of value in reducing the reactions to the subsequent dose of live vaccine. Consideration, however, should also be given to the unusual local and systemic reactions which may sometimes occur when children who have received killed vaccine are exposed to measles or given a dose of live vaccine a number of years later (Fulginiti *et al.*, 1967). Such reactions, which have been reported entirely from the U.S.A., have so far occurred only in children who have had repeated doses of killed vaccine. They have not been observed in any of the children in the British trial in which only one dose of killed vaccine was given and was followed after a relatively short period of a month by live vaccine. Nevertheless, it would be wise not to use killed vaccine at all until more information is available about the mechanism of such reactions and how they can be avoided.

Though the results so far obtained show that substantial protection was well maintained over a period of almost three years, it is intended to continue the trial to obtain information on the duration of immunity for longer periods. This will indicate whether reinforcing doses should be given and, if so, the most suitable time for their administration.

But though this question of the duration of immunity cannot be answered immediately, it is quite clear from the results so far obtained from this trial that immunization with a single dose of live measles vaccine, if practised on a wide scale throughout Britain, should bring about a striking diminution in the incidence of the disease. Such a reduction has already been achieved in the U.S.A., where extensive vaccination has been in progress on an increasing scale since 1963 (National Communicable Diseases Center, 1967).

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