Papers and Originals

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

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

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During the early part of 1964 a trial of measles vaccines was made in Britain under the auspices of the Medical Research Council's Measles Vaccines Committee. About 300 children took part and four vaccination schedules were used, involving two different live attenuated vaccines and one inactivated (killed) vaccine. In two of the schedules live vaccine was preceded by a single dose of killed vaccine and in the other two live vaccine was given alone. Each schedule produced satisfactory antibody responses, and vaccination reactions were in general not severe (Medical Research Council, 1965).

This preliminary trial has now been followed by a much larger investigation to assess the value of the vaccines for general use. This second trial was started in the autumn of 1964, and the preliminary results reported here are those obtained in the first six months after vaccination during the measles epidemic of 1964–5. Relevant references to previous work on measles vaccines were made in the preceding report and are not repeated here.

* 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 Great Britain.

Measles Vaccines Committee: Professor D. G. Evans (chairman), Professor W. Gaisford, Professor C. H. Stuart-Harris, Dr. J. Stevenson Logan, Dr. K. McCarthy, Dr. C. L. Miller, Professor Sir Alan Moncrieff, Dr. T. M. Pollock, Dr. Ian Sutherland, Dr. D. Thomson, Dr. G. I. Watson, Sir Graham Wilson, and Dr. F. T. Perkins (secretary).

Medical Officers of Health: Dr. A. Anderson (Middlesex County Council 9), Dr. J. H. Briscoe-Smith (Westminster), Dr. J. K. Brown (Greenwich), Dr. A. D. C. S. Cameron (Hammersmith), Dr. J. R. Campbell (Middlesex County Council 2), Dr. W. Cormack (Harrow), Dr. E. M. Cran (London County Council 1), Dr. O. Dobson (Hillingdon), Dr. R. G. Davies (Hackney), Dr. R. W. Elliott (West Riding of Yorkshire), Dr. J. E. Epsom (Southwark), Dr. T. McL. Galloway (West Sussex), Dr. J. L. Gilloran (Edinburgh), Dr. E. Grundy (Brent), Dr. W. G. Harding (Camden), Dr. A. Hutchison (Hull), Dr. W. D. Hyde (Enfield), Dr. S. King (Islington), Dr. G. W. Knight (Hertford), Dr. J. T. R. Lewis (Wandsworth), Dr. R. L. Lindon (Hounslow), Dr. J. Stevenson Logan (Southend-on-Sea), Dr. A. McGregor (Southampton), Dr. J. Madison (Middlesex County Council 10), Dr. L. A. Matheson (Northern Region, Surrey), Dr. C. Metcalfe Brown (Manchester), Dr. A. Mower-White (London County Council 7), Dr. A. M. Nelson (Richmond-on-Thames), Dr. H. L. Oldershaw (London County Council 2), Dr. J. L. Patton (Harringey), Dr. G. E. B. Payne (Middlesex County Council 7), Dr. W. Powell Phillips (Cardiff), Dr. P. G. Roads (Portsmouth), Dr. I. H. Seppelt (Ealing), Dr. A. B. Stewart (London County Council), Dr. A. L. Thrower (Lambeth), Dr. F. R. Waldron (Lewisham), Dr. H. S. Wallace (London County Council 8), Dr. J. F. Warin (Oxford), Dr. M. Watkins (Barnet), Dr. R. W. Watton (Tower Hamlets), Dr. J. H. Weir (Kensington and Chelsea), Dr. G. S. Wigley (Middlesex County Council), Dr. H. C. M. Williams (Southampton), Dr. R. C. Wofinden (Bristol).

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.

Serological studies were made by: Dr. Mairin Clarke, Division of Immunological Products Control, Medical Research Council Laboratories, Hampstead, London N.W.3, Dr. P. Benson (Guy's Hospital), Dr. L. A. Charrett (Medical Officer of Health, Slough), Dr. A. Hutchison (Medical Officer of Health, Hull), Dr. M. Schapira (General Practitioner, Keighley), Dr. C. L. Sharp (Medical Officer of Health, Bedford).

Pilot studies were made by: Dr. Hugh Falkner (Caversham Centre, London).

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

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

The report was prepared by: Professor D. G. Evans, Dr. C. L. Miller, Dr. F. T. Perkins, Dr. T. M. Pollock, and Dr. Ian Sutherland.

General Plan

The trial was co-ordinated from the Medical Research Council Laboratories, Hampstead, according to a uniform plan. The field work was conducted by the local health authorities in the following areas: London County Council Divisions 1–9,[1] Middlesex County Council areas 1–9,[1] Bristol, Cardiff, Edinburgh, Hull, Manchester, Oxford, Portsmouth, Southampton, Southend-on-Sea, West Riding of Yorkshire, West Sussex. The local health authorities obtained the parents' consent for the children to take part, allocated them to the vaccinated and unvaccinated groups, gave the vaccine, and conducted the follow-up. Parents were invited to register for the trial those children between 10 months and 2 years of age who had not previously had measles. On registration each child was allocated according to date of birth to one of the following three groups to receive (*a*) killed vaccine followed one month later by live vaccine, (*b*) live vaccine alone, and (*c*) no vaccine. Exceptions to this procedure were made in Cardiff and the West Riding, where live vaccine alone was not given and the allocation of the children was made to the other two groups only.

During the third week after the live vaccine was given efforts were made to contact the parents of all children, both vaccinated and unvaccinated, to record any symptoms which had occurred since the vaccination date. Further similar contacts were made at three and six months after giving the live vaccine to record the incidence of measles. On most occasions contacts were made personally by the nurse or health visitor at the clinic or in the home, but when this was difficult contacts were made by postal inquiry or telephone.

At the outset of the investigation the general practitioners in the various areas were told about the trial and asked to help. For each child, whether vaccinated or not, a follow-up form was sent to the doctor concerned, who was asked to attach the form to the appropriate National Health Service record and to return it if the child developed measles. If the doctor did not return the follow-up form of a case reported by the health visitor the doctor was then asked whether he had seen the child during the incident and could confirm the diagnosis.

In assessing the protective effect of the vaccination schedules all the reported cases of measles were analysed. In assessing similarly of groups and intensity of follow-up sufficient information was obtained from a representative sample of about 11%, consisting of all those children whose surname began with the

[1] These areas and divisions are now included in the Greater London Council, Hertfordshire, and Surrey.

letter B. The same sample was also used in assessing the incidence of symptoms after vaccination, apart from convulsions, the incidence of which was examined for all participants.

The results obtained from the representative sample were processed by the Medical Research Council Computer Services Centre.

Allocation of Children

Except in Cardiff and the West Riding, children born from the 1st to the 10th day of each month were allocated to receive killed followed by live vaccine, those born from the 11th to the 20th day to receive live vaccine alone, and those born from the 21st to 31st day to remain unvaccinated. In Cardiff and the West Riding, children born from the 1st to the 20th day of each month were allocated to the killed/live-vaccine group and those born from the 21st to the 31st day to the unvaccinated group.

Children were ineligible for participation in the trial if there was a history of fits, eczema, asthma, sensitivity to egg, treatment with chemotherapeutic agents or steroids, other current immunizations, or illness at the time they were called for vaccination. Those who failed to keep their appointments for either killed or live vaccine were offered a second appointment within two weeks, and if they failed to keep this they were not vaccinated. All children who defaulted and those who were excluded because of their history were, however, followed up in the same way as those who took part. This was done to verify that the incidence of measles in the excluded children was similar to that in the unvaccinated control group, and consequently that their exclusion had not invalidated the results.

Vaccination

The live attenuated vaccine used was prepared by Glaxo Laboratories from the Schwarz strain of measles virus derived from the Enders-Edmonston B strain. The dose of 1 ml. contained $10^{3.5} \pm 10^{0.3}$ TCD_{50} of measles virus. The titre of the vaccine was checked before it was issued to the local health authorities and rechecked by titrating samples of returned unused vaccine. All titrations were satisfactory. The vaccine was issued in the dried form along with distilled water to be used as diluent. The killed vaccine was prepared by Pfizer Ltd. from the Enders-Edmonston B strain and was aluminium-hydroxide-adsorbed. It was in the liquid form and the dose used was 0.5 ml.

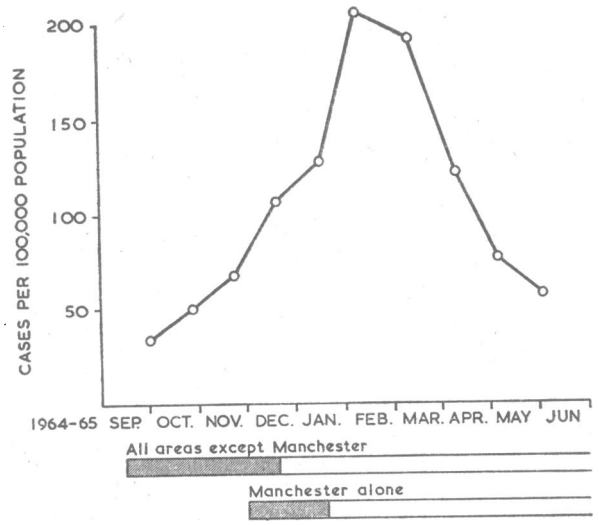

Chart showing notified incidence of measles per 100,000 population in all areas taking part in the trial. The horizontal blocks indicate the period of the trial and the shaded areas the period during which the inoculations were given.

The vaccines, together with disposable syringes, were issued as required to the local health authorities; the vaccines were stored at between 2 and 10° C. and used within two weeks of being received. The killed vaccine was injected intramuscularly and the live vaccine subcutaneously. Parents were informed that fever or rash might occur in some children. The vaccines were given between the end of September and the middle of December, except in Manchester, where vaccination was completed in January. It is seen from the Chart, which gives the general course of the epidemic in the trial areas, that vaccinations were completed, apart from the Manchester area, in the early phase of the epidemic.

Serological Tests

To check that the vaccines were able to induce an adequate antibody response a small study was made in a number of children in one of the trial areas, Hull, and also in Bedford, Slough, and Keighley, where some children were vaccinated but did not take part in the main investigation. Serum samples were taken from the children before vaccination and four to six weeks after receiving live vaccine. Only those children who had no antibodies before vaccination were included in the analysis. The sera were titrated as in the previous investigation (Medical Research Council, 1965) by the haemagglutination-inhibition test, and antibody titres are expressed as international units/ml. of serum.

Of 105 children who received live vaccine alone, 92% responded with a titre of 0.25 unit or more, and the geometric mean titre was 1.5 units. Of 48 children who received killed and live vaccine, 96% responded with 0.25 unit or more, and again the geometric mean titre was 1.5 units. The responses obtained in these groups were very similar to those obtained in the previous study. (In these tests a titre of 1 unit was approximately equivalent to a dilution titre of 1:32.)

Children in the Trial

Table I shows the number of children who took part in the trial. A total of 47,041 children were registered; of these, 16,884 were allocated to receive killed and live vaccine, 13,433 to receive live vaccine alone, and 16,724 to remain unvaccinated. A smaller number of children were allocated to the live-vaccine group, because live vaccine alone was not used in two of the areas.

TABLE I.—*Children in the Trial*

Group	Total Registered	Not Eligible		Defaulters from Vaccination		Final Total in Group	
		No.	%	No.	%	No.	%
Killed/live vaccine	16,884	2,413	*14*	3,846	*23*	10,625	*63*
Live vaccine ..	13,433	1,480	*11*	2,376	*18*	9,577	*71*
Unvaccinated control	16,724	396	*2*	0	*0*	16,328	*98*
Total ..	47,041	4,289	*9*	6,222	*13*	36,530	*78*

For the various reasons previously mentioned 14% of the children allocated to receive killed and live vaccine and 11% of those allocated to receive live vaccine alone were considered ineligible. Fewer children in the control group were classified as ineligible, only 2%, and this was because the decision on eligibility was usually taken when the child attended for vaccination.

Of the children allocated to receive killed and live vaccine, 23% failed to complete the vaccination, though some of these received killed vaccine only, and of those allocated to receive live vaccine alone 18% failed to attend. After excluding those who defaulted from vaccination and those who were considered ineligible there remained a total of 36,530 children, 10,625 in

the killed/live-vaccine group, 9,577 in the live-vaccine group, and 16,328 in the unvaccinated control group.

Similarity of Groups

Some characteristics which might have affected the risk of subsequent exposure to measles were examined to test the similarity of the groups at the outset of the trial. This examination was done with the representative sample of children, and the results are given in Table II. It is seen that the mean family size and also the history of exposure to measles in siblings were very similar for the three groups, indicating that the subsequent exposure to measles in the home was unlikely to be different in vaccinated and control children. It was thought that the frequency of exposure outside the home might be affected by attendance at day nurseries, but the proportion of children attending these nurseries was small, only 2%, and was the same in each group. The groups were also similar with regard to the proportions who had been previously immunized with other vaccines.

TABLE II.—*Similarity of the Groups at the Outset of the Trial from the Representative Sample*

Group	No. in Sample	Mean Family Size	Previous Measles in Siblings				Attending Day Nursery		Previous Immunization with Triple and/or Polio Vaccine	
			Under 5 Years		Over 5 Years					
			No.	%*	No.	%*	No.	%	No.	%
Killed/live vaccine	1,127	2·07	85	*17*	517	*76*	20	*2*	1,065	*94*
Live vaccine ..	1,015	2·09	90	*19*	465	*78*	16	*2*	958	*94*
Unvaccinated control	1,732	2·17	177	*21*	790	*74*	35	*2*	1,563	*90*

* Percentage of total siblings of this age.

The intensity of the follow-up was also similar for the three groups, as may be seen from Table III, which gives, for the representative sample of children, the proportion contacted at three weeks, three months, and six months. It is evident that on each of the three occasions, and in each of the three groups, the proportion contacted was high, always more than 90%.

TABLE III.—*Follow-up of Children at Three Weeks, Three Months, and Six Months from the Representative Sample*

Group	No. in Sample	Percentage Followed Up at 3 Weeks by			Percentage Followed Up by all Methods at		
		Personal Contact	Telephone	Letter	3 Weeks	3 Months	6 Months
Killed/live vaccine ..	1,127	*88*	*9*	*1*	*98*	*97*	*95*
Live vaccine	1,015	*87*	*9*	*2*	*98*	*94*	*95*
Unvaccinated control ..	1,732	*79*	*9*	*6*	*94*	*93*	*92*

More detailed information of the methods used for follow-up is given for the three-week period in Table III. Although in general the three groups were treated in a similar way, it is noted that in the control group fewer children were contacted personally than in either of the vaccinated groups. These differences were probably due to parents of vaccinated children being asked at the vaccination session to return to the clinic for the first follow-up.

Symptoms Reported at the Third-week Follow-up

Table IV gives, for the representative sample of children, data on those who were reported by their parents as having been unwell during the three weeks after vaccination—that is, at the time when reactions from the vaccine were most likely. Confirmed cases of measles during the three weeks are excluded, but are analysed in Table VII. Convulsions are also dealt with separately in Table V.

It is evident from Table IV that many children in all three groups were unwell and that the proportion was greatest in the live-vaccine group (61%), less in the killed/live-vaccine group (54%), and least in the unvaccinated group (38%). The parents' reports of a child being unwell were associated with numerous symptoms, such as loss of appetite, vomiting, disturbed sleep, malaise, rash, fever, respiratory symptoms, and diarrhoea. Of these symptoms loss of appetite, vomiting, disturbed sleep, malaise, rash, and fever, which are referred to in Table IV, were more frequent in the vaccinated groups than in the unvaccinated children, and tended to be most frequent in those who received live vaccine alone. The incidence of fever is probably underestimated, since reports were not based on routine temperature readings. It was also found that respiratory symptoms and diarrhoea, which are not included in Table IV, occurred with similar frequency in each of the three groups.

Despite the greater proportion of vaccinated children who were unwell, their symptoms were not usually sufficiently disturbing for them to be seen by the family doctor. Only 11% of the children in each vaccinated group were reported as having been seen by the doctor during the three-week period, and in fact this proportion was slightly less than the proportion of unvaccinated children seen by the doctor. A few children in each group were admitted to hospital during the three-week period, but the numbers were too small for a useful comparison between the groups.

Information about convulsions occurring within the first three weeks after vaccination is given in Table V for all the trial children and not merely for the sample. Only those convulsions are recorded which were definitely confirmed by the doctor. The incidence of convulsions was greatest in the

TABLE IV.—*Symptoms During the First Three Weeks' Follow-up from the Representative Sample, Excluding Cases of Measles and Convulsions*

Group	No. in Sample	Children Unwell		Symptoms								Seen by Family Doctor		Admitted to Hospital	
				Off Food/ Vomiting		Disturbed Sleep/Malaise		Rash		Fever					
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Killed/live vaccine	1,127	608	*54*	281	*25*	448	*40*	154	*14*	42	*4*	120	*11*	4	*0·4*
Live vaccine	1,015	620	*61*	317	*31*	454	*45*	190	*19*	65	*6*	111	*11*	2	*0·2*
Unvaccinated control	1,732	665	*38*	268	*15*	368	*21*	22	*1*	20	*1*	249	*14*	7	*0·4*

TABLE V.—*Convulsions During the First Three Weeks' Follow-up in all Trial Children*

Group	No. of Children	Convulsions		No. Associated with Fever	No. with Family History of Fits	Day of Convulsion After Vaccination												
		No.	Rate/1,000			0	3	4	5	6	7	8	9	10	11	12	13	14–21
Killed/live vaccine ..	10,625	7	0·7	7	1			2				1					1	3
Live vaccine	9,577	18	1·9	17	3	1				3	3	2	3				1	5*
Unvaccinated control ..	16,328	5	0·3	5	2		1		1					1				2

* One child had an afebrile convulsion and was subsequently found to be an epileptic.

group given live vaccine alone (1.9/1,000), less in the group given killed and live vaccine (0.7/1,000), and least in the control group (0.3/1,000). All but one of the cases were associated with fever, and the greater incidence in those given live vaccine alone would therefore appear to be referable to the greater likelihood of fever in this group. Furthermore, a high proportion of the convulsions after live vaccine alone occurred between six and nine days—that is, when fever induced by the vaccine was most likely (Medical Research Council, 1965). In contrast there was no similar concentration of cases in the group given killed and live vaccine or in the control group, and in view of this it is probable that there was little or no association between convulsions and vaccination when live vaccine was preceded by killed vaccine.

It is also noted from Table V that four of the vaccinated children who had convulsions had a family history of fits. It is probable that the incidence of convulsions would have been less if children with a family history of fits had been excluded from the trial and not merely those with a personal history.

Protective Effect of Vaccines in all Trial Children

Table VI shows the cases of measles reported by the parents and those seen and diagnosed by the doctor. Of the total cases reported the doctor saw about 60%, and, of these, confirmed the parents' diagnosis in 93% in the control group, 64% in the killed/live-vaccine group, and 70% in the live-vaccine group. These differences in the proportion confirmed between vaccinated and control children can be attributed to the fact that many cases in the vaccinated children were of a mild and transitory nature, having been modified by immunization. That vaccination does modify the disease is supported by the results discussed later and shown in Table X.

TABLE VI.—*Cases of Measles in All Trial Children Reported by Parents and Those Seen and Diagnosed by a Doctor During the Six Months' Follow-up in All Trial Children**

Group	No. of Children	No. of Cases of Measles Reported by Parent	Cases Reported by Parent and Seen by Doctor		Cases Seen by Doctor and Diagnosed as Measles	
			No.	%	No.	%
Killed/live vaccine ..	10,625	365	200	*55*	128	*64*
Live vaccine	9,577	395	224	*57*	156	*70*
Unvaccinated control ..	16,328	2,679	1,653	*62*	1,531	*93*

* Provisional figures; doctors' reports are still being received.

The results of analysis of the protective effect of vaccination based on the confirmed cases during the six-month period are given in Table VII. It is evident that substantial protection was induced by both vaccination schedules. The incidence of measles in the group given live vaccine was about one-sixth, and that in the group given killed and live vaccine about one-eighth of that in the unvaccinated group. There was, however, no statistically significant difference in the degree of protection shown by the two schedules. It may be concluded that vaccination by either method gave a degree of protection against measles of about 85% over the six-month period so far studied. This conclusion is necessarily based on the cases seen and confirmed by the doctor, but a similar conclusion is also evident from the total cases of measles reported by the parents (see Table VI).

TABLE VII.—*Incidence of Measles During One Month and Six Months After the Vaccination Date in All Trial Children*

Group	No. of Children	Confirmed Cases of Measles Occurring			
		During 1st Month		During Whole 6 Months	
		No.	Rate/1,000	No.	Rate/1,000
Killed/live vaccine ..	10,625	12	1·1	128	12
Live vaccine	9,577	31	3·2	156	16
Unvaccinated control ..	16,328	166	10·2	1,531	94

The incidence of confirmed measles during the first month after vaccination has also been analysed, and the results are included in Table VII. The incidence was sufficiently high during this period for some conclusions to be drawn regarding the early protective effect of vaccines. In both vaccinated groups protection against measles was evident, especially in the group given killed and live vaccine. The greater incidence in those given live vaccine alone may have been due either to a slower development of immunity or to some of the vaccination reactions in this group having been diagnosed as measles.

An analysis was also made of the incidence of measles during the six months after the vaccination date in those children who were excluded from the trial in order to verify that their exclusion had not invalidated the conclusions regarding the protective effect of vaccination. The results of this analysis are shown in Table VIII, which gives the incidence in those children who were ineligible, in those who defaulted completely, and in those who defaulted after having had killed vaccine only. Also included in Table VIII for comparison is the incidence of measles in the control group. It is seen that the incidence in the children who defaulted completely and in those who were ineligible was very similar to that in the control group. It is also seen that the incidence in the children who defaulted after receiving killed vaccine was slightly less than that in the control group, perhaps because the killed vaccine alone was having some protective effect. In general it may be concluded that the defaulting and ineligible children were as susceptible to measles as the unvaccinated control group, and thus it is unlikely that their exclusion from the main trial materially affected the results of the analysis.

TABLE VIII.—*Incidence of Measles Among Those Children Excluded from the Main Analysis, During the Six Months After the Vaccination Date*

Group	No. of Children	Cases of Measles Confirmed by General Practitioner	
		No.	Rate/1,000
Ineligible for vaccination	4,289	408	95
Defaulter unvaccinated	5,411	533	99
Defaulter given killed vaccine	792	60	76
Unvaccinated control	16,328	1,531	94

Protective Effect of Vaccines in Children Known to be in Contact with Measles at Home

An analysis was made of those children in the representative sample who were known to be in contact with measles in the home during the six months after vaccination, and the results are given in Table IX. This analysis includes all cases of measles reported by the parents, and not only those seen and confirmed by the doctor. It is evident that in each group a similar proportion were exposed to measles in the home. It is also evident that both vaccination schedules produced substantial and similar protection against the disease; the attack rate was 9% in the killed/live-vaccine group and 6% in the live-vaccine group, compared with 83% in the unvaccinated controls.

TABLE IX.—*Incidence of Measles During the Six Months' Follow-up in Children in Contact with the Disease at Home (from the Representative Sample)*

Group	No. of Children in Known Contact with Measles at Home	% of all Children in the Sample	Cases of Measles Following Home Contact	
			No.	% Attack Rate
Killed/live vaccine ..	85	*8*	8	*9*
Live vaccine	90	*9*	5	*6*
Unvaccinated control..	119	*7*	99	*83*

Severity and Complications of the Disease in Vaccinated and Unvaccinated Children

For each case of measles the doctor was asked to report whether he considered the disease mild, moderate, or severe, and the results of these assessments are given in Table X, which also includes those cases requiring four or more visits by the doctor.

TABLE X.—*Degree of Severity of Measles in Cases Confirmed by the Doctor*

Group	No. of Cases	Doctor's Assessment of Degree of Severity						4 or More Home Visits by Doctor	
		Mild		Moderate		Severe			
		No.	%	No.	%	No.	%	No.	%
Killed/live vaccine	128	99	77	26	20	3	2	6	5
Live vaccine ..	156	120	77	35	22	1	1	8	5
Unvaccinated control	1,531	728	48	737	48	66	4	149	10

The proportion of severe cases was small in all three groups, and was insufficient to make an informative comparison between the groups. From the figures in the mild and moderate categories, however, it is evident that vaccination by both schedules substantially modified the attack. For example, in each of the vaccinated groups there were 77% of mild cases, compared with 48% in the controls. The modifying effect of vaccination is also indicated by the proportion of cases visited four or more times by the doctor; in the control group the proportion was twice that in either of the vaccinated groups.

An analysis was also made of the nature of the complications which occurred in those cases confirmed by the doctor. For each case the doctor was asked to report whether the disease had been accompanied by bronchitis, pneumonia, otitis media, convulsions, or any other complication. The incidence of specific complications is given in Table XI. It is seen that bronchitis was the most frequent complication, and that its incidence was similar in the three groups. The remaining complications were too few for any conclusions to be drawn regarding their relative incidence in the groups.

A comparison, however, may be made between the incidence of convulsions associated with an attack of measles and that associated with live vaccine given alone. It is seen from Table XI that convulsions occurred in 14 of the 1,815 cases of measles, an incidence of 7.7/1,000, whereas Table V shows that 18 convulsions occurred in the 9,577 children given live vaccine alone, an incidence of 1.9/1,000. Clearly there is a much greater risk of convulsions occurring from an attack of measles than after an injection of live vaccine.

It is also seen from Table XI that 23 children with measles were admitted to hospital—22 in the control group and one in the live vaccine group. There was no case of encephalitis associated with any of the attacks of measles, but there were three deaths from pneumonia, all occurring in unvaccinated children.

Summary and Conclusions

The trial described in this report was conducted in 32 different areas, and 36,530 children took part. It was the first large-scale trial of measles vaccines in Great Britain, and the findings are thus relevant to the control of measles in this country.

Two immunization procedures were investigated—live attenuated vaccine given alone and a single dose of killed vaccine followed one month later by live vaccine. The trial was planned so that a valid assessment could be made of the frequency and degree of severity of the reactions following vaccination and also the ability of the vaccines to produce protection in the face of an epidemic. Children in the susceptible age-group of 10 months to 2 years, whose parents consented, were allocated by an effectively random method to one of three groups to receive (*a*) killed vaccine followed by live vaccine, (*b*) live vaccine alone, and (*c*) no vaccine.

After excluding those children who were ineligible and those who defaulted, 10,625 received killed and live vaccine, 9,577 live vaccine alone, and 16,328 remained unvaccinated. The groups were shown to be similar in their mean family size, in the history of exposure to measles in siblings, and in other characteristics.

After the live vaccine had been given, all children, both vaccinated and unvaccinated, were followed up for six months through the measles epidemic of 1964–5. The intensity of the follow-up was similar for all three groups. Records were taken of reactions occurring in the three weeks following the vaccination date of live vaccine and of the cases of measles occurring during the whole six-month period. It is intended to continue the trial through at least one more epidemic of measles to investigate the duration of immunity, and already records of the nine months' follow-up have been received.

It was found that the live vaccine when given alone caused more illness than when it was preceded by killed vaccine, but in general the illnesses were not serious. The symptoms attributable to vaccination included loss of appetite, vomiting, disturbed sleep, malaise, rash, and fever. A few cases of convulsions occurred in all three groups, and all but one were associated with fever. The time of the occurrence of convulsions in relation to the time of vaccination indicated that live vaccine when given alone was responsible for some of the cases but not when it was preceded by killed vaccine. It was considered that a convulsion following live vaccine was part of a general febrile reaction which is common in children of this age and is not serious. Furthermore, it was shown that there was much less risk of convulsions after an injection of live vaccine than from an attack of measles. However, the findings suggest that live vaccine alone should not be given to children with a history, or family history, of convulsions.

In assessing whether the reactions to vaccination contraindicate the use of these measles vaccines on a large scale, it was found that although a few reactions caused disquiet the great majority of children either remained well or had only trivial complaints. There was also no indication that the reactions increased the medical care required, since the proportion of children visited by the doctor or admitted to hospital during the three weeks following vaccination was no greater in the vaccinated groups than in the unvaccinated controls.

Both vaccination schedules gave substantial protection against measles. Over the six-month period the number of cases seen and diagnosed by the doctor was 128 in the killed/live-vaccine group, 156 in the live-vaccine group, and 1,531 in the unvaccinated group. The corresponding attack rates per 1,000 children were 12, 16, and 94, showing a reduction in the incidence of the disease by vaccination of about 85%. Furthermore, those cases which occurred in vaccinated children were on the average milder than those in unvaccinated children.

TABLE XI.—*Specific Complications Associated with Confirmed Cases of Measles*

Group	Total No. of Confirmed Cases	Specific Complications								Cases Admitted to Hospital	No. of Deaths
		Bronchitis		Pneumonia		Otitis Media		Convulsions			
		No.	%	No.	%	No.	%	No.	%		
Killed/live vaccine	128	20	16	0	0	5	4	2	2	0	0
Live vaccine	156	29	19	0	0	2	1	2	1	1	0
Unvaccinated control	1,531	304	20	10	1	57	4	10	1	22	3

A similar reduction in incidence was shown among those children who were known to be in contact with measles in their own homes and presumably exposed to heavy infection. The attack rates in a representative sample of children exposed at home were 9% in the killed/live-vaccine group, 6% in the live-vaccine group, and 83% in the unvaccinated group.

Those children who defaulted from vaccination and those who were ineligible were also followed up in the same way as the children who took part in the trial. It was shown that the excluded children were in general as susceptible to measles as the unvaccinated control group, and it was thus most unlikely that their exclusion had materially affected the results of the analysis of the main trial.

Although vaccination was highly effective it was unable to protect all children from measles. It is true that a few of the cases occurred soon after vaccination, perhaps before immunity had had time to develop, but most of them occurred later and were probably due to the inability of some children to produce an adequate antibody response. This view is supported by the results of the serological study in which a small proportion of children vaccinated by each method showed no antibody response. It is possible that a less attenuated live vaccine would produce protection in a greater proportion of children, but there is the probability that it would also produce more pronounced reactions and in consequence be less suitable for large-scale routine use.

In considering which of the two procedures studied is the more suitable to use in vaccinating against measles, the following points should be taken into account. Both live vaccine alone and killed vaccine followed by live give a substantial and similar degree of protection in normal children aged 1 to 2 years, but it is not yet known how long the immunity will last. Killed vaccine given before live vaccine has the advantage of reducing the frequency of reactions including convulsions. On the other hand, vaccination with live vaccine alone requires only one injection.

But no matter which procedure is chosen it is clear from the results of this trial that vaccination, if done on a large scale, could produce a substantial reduction in the incidence of measles in this country. Such a reduction would undoubtedly lighten the burden placed on family doctors and parents, especially in an epidemic year, when approximately half a million cases occur.

The Measles Vaccines Committee of the Medical Research Council thanks Mrs. A. Allchin and her staff of the Medical Research Council Laboratories, Hampstead, London, for co-ordinating the clerical work of the trial; Miss C. Bramley, of the Medical Research Council Computer Services Centre, for the computer programme; and Mr. H. Ward, Mrs. J. Hall, and Miss R. Porter, of the Division of Immunological Products Control, Medical Research Council Laboratories, Hampstead, London, for the distribution of vaccines.

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Risk of Serious Infection Following Splenectomy

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The possibility that splenectomy might predispose to infection was first reported by King and Schumacker (1952), and since then there have been several communications on this subject. Even so, there is no accepted opinion regarding the numerical risk of this complication nor whether it is restricted to certain age groups or specific conditions for which splenectomy is performed. It is generally conceded that any risk is greatest if splenectomy is performed in infancy (Huntley, 1958), especially if the underlying disease itself carries a high risk of infection (Robinson and Sturgeon, 1960), but infections have followed splenectomy for traumatic rupture in adults.

Characteristically such infections have been acute septicaemic illnesses often leading to death of the patient from adrenal haemorrhage within a few hours of onset, and the organisms most frequently concerned have been the pneumococcus and *Haemophilus influenzae*. Infections have not always been septicaemias; Gofstein and Gellis (1956) reported a fatal case of tracheobronchitis, and the activation of tuberculosis (Edwards, 1951; MacPherson, 1959) and the dissemination of lupus erythematosus (Carpenter *et al.*, 1959) have been attributed to splenectomy. A third feature has been a recurrent pattern of infections in some patients (Lowdon *et al.*, 1962; Horan and Colebatch, 1962).

It is estimated that 80% of serious infections occur within two years of operation (Smith *et al.*, 1957; Horan and Colebatch, 1962), and Gordon (1960) believes that the shorter the interval the worse the prognosis. Doan *et al.* (1960), however, reported serious infections in three adults between five and eight years after operation.

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Present Study

Because we had recognized four cases of severe infection in 75 children subjected to splenectomy (Lowdon *et al.*, 1962), and because there was no accepted opinion concerning the existence, frequency, or nature of increased susceptibility we felt that a review of a large group of cases was indicated.

We therefore made a direct approach to all regional senior administrative medical officers and professors of surgery in England and Wales asking for their co-operation by supplying us with a list of all patients who had undergone splenectomy during 1961, whatever the reason. The year 1961 was chosen because this, at the start of the study, was the latest year for which results of the Hospital In-patient Enquiry had been published by the Central Registry Office of the Ministry of Health. In the Hospital In-patient Enquiry there were 89 cases of splenectomy; therefore we expected 890 for the whole year, but in fact 1,167 were notified.

Comparison of the 10% sample with the total group showed two significant differences. The age distribution of the "sample" was low, while the number of cases in the "total" group where splenectomy had been performed as part of some other major operation was high. These we attributed to the