VACCINATION AGAINST MEASLES IN GENERAL PRACTICE

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There have been several reports from the U.S.A. of trials of live measles vaccine prepared from the Edmonston strain of virus (Katz *et al.*, 1960; Enders *et al.*, 1962; Markham *et al.*, 1962), and two recent reports of studies of a British vaccine also derived from this strain (Collard *et al.*, 1961; Aldous *et al.*, 1961). While these last two studies were in progress it became apparent that an epidemic of measles was developing in England, and it was decided to carry out a study of the use of live measles vaccine in general practice.

The objects of the study were to observe the protective effect of the vaccine in pre-school children living in families where the degree of exposure to natural measles could be assessed, and to record reactions to the vaccine.

Materials and Methods

Plan of the Trial.—In order to obtain an adequate number of home exposures to measles in vaccinated children, families were selected which had at least two children—one of pre-school age and one of primary-school age. After setting one-third of all families on one side as controls, vaccination was offered to the remaining families for the pre-school children only. The older school-age children were left unvaccinated in the anticipation that they would develop measles by contact with cases at school. They would then provide a natural challenge of the immunity of the pre-school children at home, and a comparison would be possible of the incidence of measles in home-exposed vaccinated and control populations.

Vaccine.—The measles vaccine consisted of living attenuated measles virus, Edmonston strain (Enders *et al.*, 1962). Only one batch, MV-3C, was used, the preparation and testing of which has been described in detail previously (Goffe and Laurence, 1961). The freeze-dried vaccine was reconstituted with 1 ml. of sterile distilled water immediately before use and was injected subcutaneously.

Study Population and Allocation to Groups.—The children in this study were patients of a partnership of six doctors, and nearly all of them lived on a housing estate on the outskirts of London. Each doctor's list was searched for families containing at least one child born between January 10, 1956, and July 1, 1960 (pre-school age), and another born between September 1,

1949, and January 9, 1956 (primary-school age). The names, ages, and measles history of all members of each family were entered on a record card. Families were then allotted to vaccination or control group in the following way. Each doctor's list was taken in turn, ranking the families in order of size; families were allocated in threes by random selection in the ratio of two to vaccination and one to control groups. A letter was sent to the mother of each family selected for vaccination offering vaccine for the measles-susceptible pre-school children, and the great majority accepted.

Vaccination and Follow-up.—A total of 154 children were vaccinated either at the doctors' consulting-rooms or at home between February 3 and 10, 1961. Only children in the vaccinated group were observed for reactions. Each vaccinated child was seen on or about the 12th day, or earlier if the parents had so requested, and reactions to the vaccination were recorded. During the six months after vaccination each doctor recorded every case of measles which was reported to him in any child in the families under study. At the end of this period every family under study in whom measles had not been recorded during this time was contacted to ensure that no case of measles had been missed. The information collected during the study was transferred to punch cards and analysed.

Exclusions from the Study.—After being allotted to the vaccination group some families were excluded when it was found that the pre-school children had, in fact, had measles. About the same proportion of control families were excluded when their measles histories were checked at the six-months follow-up. Children originally allocated to the vaccination group whose parents did not wish them to be vaccinated, and those who were absent or were suffering from intercurrent illness at the time of vaccination, were added to the control group for follow-up.

Results

The allocation procedure resulted in two groups of unequal size but having a similar age composition (Table I). The two groups also had similar distributions of family size and of pre-vaccination history of measles in the family.

TABLE I.—*Age Distribution of Vaccinated and Unvaccinated Children*

Children	Age in Months						Total
	7-12	13-18	19-24	25-36	37-48	49-60	
Vaccinated .. {	10 6.5%	13 8.4%	18 11.7%	41 26.6%	39 25.3%	33 21.4%	154
Unvaccinated {	5 4.4%	15 13.2%	11 9.6%	27 23.7%	31 27.2%	25 21.9%	114
Totals {	15 5.6%	28 10.4%	29 10.8%	68 25.4%	70 26.1%	58 21.6%	268

$\chi^2=2.492$; 4 d.f. Not significant.

Occurrence of Measles

A total of 110 cases of measles was recorded. The protective effect of the vaccine is shown in Table II, which gives the incidence of measles in the vaccinated and unvaccinated children during the six months following vaccination. There were no cases among the 154 vaccinated children, whereas 41 (36%) of the 114 children in the control group developed measles. Table III shows the incidence of measles among those susceptible pre-school children who were in contact with a case of measles occurring in an older child of the

family. All the unvaccinated children developed measles, whereas no case occurred among home-exposed vaccinated children. The incubation period in the 25 home-exposed cases of the control group was estimated from the interval between onset of rash in the older sibling and younger index child. The mean interval was 11 days, with outside limits of 7 and 15 days.

TABLE II.—Incidence of Measles in Vaccinated and Unvaccinated Children During the Six Months Following Vaccination

	No.	No. Attacked
Vaccinated children	154	0
Unvaccinated „	114	41 (36%)

TABLE III.—Incidence of Measles in Vaccinated and Unvaccinated Pre-school Children after Exposure to Measles in the Home

	Vaccinated	Unvaccinated
No. of families in which school-age children developed measles	30	21
No. of susceptible pre-school children exposed	31	25
No. of cases of measles developing	0	25
Attack rate percentage	0	100

The possibility of secondary cases among susceptible contacts of vaccinated children was examined. A total of 54 cases of measles occurred in the school-age groups between February 15, one week after the last vaccination, and the end of April. Thirty of these were family contacts of vaccinated children and 24 came from control families. The distribution of the cases in time was similar for the two groups. Seven cases occurred in siblings of vaccinated children within 30 days of giving vaccine, but during the same period six cases occurred in the corresponding control population.

Vaccination Reactions

Background.—Vaccination was given at a time when the epidemic prevalence of measles was increasing. Eight cases of measles were recorded in the control population during the period when the vaccinated group was being observed for reactions to the vaccine.

Fever and Rash.—Table IV shows the frequency of reactions to vaccination. Of the 154 vaccinated children, 72% developed fever, mostly on the sixth to eighth day after vaccination. The mean duration of fever was 3.5 days. Rash was observed in 62% of the children,

TABLE IV.—Frequency of Reactions to Vaccination

No. Vaccinated	No. with Reaction	Local Reaction	Fever	Rash	Other
154	122	0	112 (72%)	96 (62%)	49 (32%)

at a slightly longer interval after vaccination. The Chart contrasts the distribution of intervals between vaccination and onset of fever and rash. The rash, which was morbilliform in appearance, generally persisted for one to two days; no rash lasted more than five days.

Other Reactions.—The vaccine did not cause any reactions at the site of injection. Koplik spots were seen in four children, but as these were not looked for specifically the actual incidence in the vaccinated children is unknown. Coryzal symptoms, which started about four days after vaccination, occurred in 18 children. They were mostly mild, but sometimes were accompanied by mucopurulent discharge from the eyes, a purulent post-nasal discharge, and cough. In four

cases the cough was troublesome and disturbed the child's sleep; four children had nocturnal delirium when the fever was at its height. Most of the other reactions occurred from the sixth to ninth day after vaccination. Six children had general symptoms—listlessness, irritability, and anorexia—of varying degree for three to five days. Five children had repeated vomiting, and in one child this was accompanied by diarrhoea. At the onset of the fever five children had a convulsion. Two were

Frequency distribution of intervals from vaccination to onset of febrile response and appearance of rash. Onset of fever in 112 cases—open columns. Onset of rash in 96 cases—black columns.

known epileptics who were having anticonvulsant treatment; the other three had not previously suffered from fits, although two of them had a family history of convulsions. Follicular tonsillitis was observed in 16 children. Six developed otitis media, and three had severe infection of the lower respiratory tract. Altogether 32 (20%) children had reactions which were judged to be severe, including 10 whose respiratory infections required chemotherapy.

Discussion

The primary object of the present study was to measure the protective effect of live attenuated measles vaccine used in the conditions of general practice during the winter months. The design of the trial seems to have been adequate for this purpose, although the vaccinated group differed from the control in that their parents had been offered and had accepted vaccination. It is unlikely that this selection had any material effect on the incidence of measles in the two groups, since almost all parents who had been invited to have their child vaccinated did in fact consent. No case of measles was recorded in a vaccinated child, whereas in the unvaccinated group all the pre-school children who came into contact with measles in the household developed the illness. During the epidemic, therefore, the vaccine conferred complete protection. It is not known for how long this immunity will persist, but there are good grounds for expecting it to be lifelong (Katz *et al.*, 1962).

All the vaccinated children were followed up within a 14-day period after vaccination to record the incidence and type of complications. No such follow-up was attempted in the control group, and it is possible that similar illness to that regarded as complications of vaccination occurred in the control group from other

causes. A search through the medical records, however, confirmed our impression that the conditions observed in the vaccinated children were not being reported by the control families at the time of the occurrence of the reactions. However, eight cases of measles did occur in the control population during this period. Since in other epidemiological respects the vaccinated and control populations proved homogeneous we would assume that a similar degree of exposure to wild measles took place in the vaccinated group. Hence we would expect about 12 vaccinated children also to have been infected with natural measles. The mutual influence of these simultaneous infections must remain conjectural, since there was no way of identifying the randomly occurring double event in the vaccinated population. We can only suppose that some of the reactions whose onset seemed to lie outside the normal distribution pattern (see Chart) may have been the result of wild-type infection occurring before vaccination.

The frequency of fever and rash was of the order expected from previous studies, but the incidence of the other reactions we observed seems to be at variance with previous studies (Enders *et al.*, 1962). A fifth of all vaccinated children were judged to have had severe reactions in the form of respiratory infection, marked debility, or convulsion. It is possible that latent agents, already present in the children, were activated in some way by the vaccination process, perhaps through some lowering of a general defence mechanism. Both Lepow *et al.* (1960) and Haggerty *et al.* (1960) found that complications of measles vaccination were largely infections of the respiratory tract and concluded that, since immunization was performed at the height of the respiratory disease season, many of the symptoms were due to agents other than the measles virus. Markham *et al.* (1962) found that season was a marked determinant of the reaction rate to measles vaccine and suggested that it was important to limit the use of live measles vaccine to the seasons with low incidence of respiratory illness.

Markham *et al.* also reported three instances of convulsive seizure following vaccination. In our series there were five cases of convulsion; two had a previous personal history of convulsions, two others had a family history of epilepsy, but the fifth had no family history of epilepsy and no known previous convulsive attack. According to Cockburn (1960) 4% to 7% of apparently normal children had one or more convulsions before they were 5 years old, usually in association with a febrile illness; a febrile convulsion might sometimes be set off by pertussis vaccine injections. Non-specific febrile convulsions of this nature seem to us the most likely explanation of the three attacks which occurred in children without previous experience of convulsions. Natural measles is known to be associated with transient electroencephalographic abnormalities, but these changes have been found not to occur after measles vaccine (Gibbs and Rosenthal, 1962). It seems likely, therefore, that the convulsions occurring after measles vaccination are associated with the pyrexia and are not caused specifically by the vaccine.

It was remarkable that there was no evidence of secondary cases from vaccinated children. Assuming that a vaccinated child, if excreting virus, would be most infective during the febrile stage and that the incubation period would be about 11 days, secondary cases might be expected in susceptible siblings around the 18th day after vaccinating the younger child. In fact there was

no excess of measles in the siblings of vaccinated children at this interval when compared with the incidence in the control population. Thus, in spite of the obvious resemblance between the illness occurring in a child undergoing a severe reaction to the vaccine and a mild case of natural measles, the infection induced by the vaccine virus seems to have been non-communicable.

As it is virtually certain that a non-immune child who is exposed to measles within the family will develop the disease, which, with its complications, can be a serious illness, there are good reasons for wanting to prevent measles by active immunization. The requirements of such a vaccine are that it should give solid protection with a single injection, that immunity should persist, and that a minimum of reaction be caused. The vaccine studied here fulfils the first criterion and may in time be found to satisfy the second. But, although one-quarter had no appreciable reaction at all, the severe reaction shown by one-fifth of all vaccinated children clearly rules out the general use of the vaccine in its present form. Further work is being done to produce a more attenuated virus.

Summary

Observations were made of 154 children receiving live attenuated measles vaccine and 114 control children for the incidence of measles during an epidemic. The vaccine conferred complete protection.

Three-quarters of the vaccinated children had fever and rash during the second week after vaccination. One-fifth had a more severe reaction. The significance of the reactions to the vaccine is discussed.

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Three British Standards have already been published for steel orthopaedic callipers. A new standard, B.S.3563, has now been prepared for orthopaedic callipers made of aluminium alloy. Though the use of aluminium alloy effects a considerable saving in weight, it is recognized that light alloy callipers of the type specified may not be suitable for some patients, who would impose heavy stresses on the appliances; for such patients steel callipers would be preferable. This specification (like others for orthopaedic appliances) was prepared at the request of the Medical Supplies Working Party of the Ministry of Health. Copies of B.S.3563, which is illustrated, may be obtained from the B.S.I. Sales Branch, 2 Park Street, London W.1. Price 6s. each. (Postage extra to non-subscribers.)