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A Comparative Study of Four Live Measles Vaccines in Israel*

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While an earlier live measles vaccine induced a high degree of immunity it also caused clinical reactions of variable severity in some vaccinated children. A number of attenuated measles vaccine strains have been developed to avoid these problems, and this paper reports the results of small-scale trials with 3 attenuated measles vaccines and a new further-attenuated vaccine on children from 9 months to over 4 years old.

All 4 vaccines produced a satisfactory serological response. The new further-attenuated vaccine (Moraten) produced less fever and fewer rashes in the vaccinated children than the other vaccines which had been extensively tested by other workers. The incidence of severe reactions and complications was low with all vaccines.

The live measles vaccine developed by Enders has been shown to induce a high degree of immunity but causes clinical reactions of variable severity in vaccinated children (Enders, 1960). Several attenuated measles vaccine strains have been developed recently with the object of producing a satisfactory antibody response and at the same time eliminating the severe clinical reactions which sometimes follow administration of the Enders vaccine. The most widely used are the Schwarz and Beckenham vaccine strains which have been included in many comparative trials in various parts of the world (Syrůček et al., 1965; Nagler et al., 1965; Hendrickse et al., 1965; Martin du Pan, 1965; Andelman, Schwarz and Spiegelblatt, 1966). The Enders Edmonston strain has been used since 1963 on an increasing scale in the USA and the Schwarz strain was employed in large-scale trials in Great Britain (Medical Research Council Measles Vaccine Committee, 1966).

Recently, a new attenuated measles virus vaccine was developed by Merck, Sharp and Dohme Laboratories, the Moraten vaccine, and this has undergone only limited trials. This paper presents the results of vaccination, and also the results of the clinical and serological follow-up of children, aged 9 months to over 4 years, vaccinated with the 4 attenuated measles vaccines: Enders Edmonston, Schwarz, Beckenham and Moraten. The study was carried out as a preliminary to the proposed vaccination of all susceptible children in Israel, and followed an immunization programme which included children 9–23 months old.

MATERIALS AND METHODS

The child population selected for the trial

A total of 444 healthy children, aged 9–48 months, evenly distributed between the two sexes and with no known past history of measles, were selected at " well-baby " clinics for this study. They came from 5 different regions of Israel: Jerusalem, Tel Aviv, Petah Tikva, Ramle and Safed. The individual records of the children were studied and supplemented by information obtained from the mothers. Children known to suffer from acute or chronic conditions incompatible with vaccination with live measles vaccine were excluded. The allocation of children into the 5 vaccination groups was randomized by giving each child a number, strictly in the sequence in which they were brought for immunization, and allocating them to one of the groups according to a previously prepared table.

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Vaccines used

The following 4 measles vaccines were used:

(1) Lyovac–Rubeovax (Lot No. 1615 H), an Enders Edmonston strain, supplied by Merck, Sharp & Dohme Laboratories, West Point, Pa., USA.

(2) Wellcovax (Batch AM23/8), a Beckenham strain, supplied by Burroughs Wellcome & Co., London, England.

(3) Mevilin–L (Batch 32/12), a Schwarz strain, supplied by Glaxo Laboratories, Ltd., Greenford, Middlesex, England.

(4) Moraten–L (Lot No. 254) supplied by Dr M. Hilleman, The Merck Institute for Therapeutic Research, West Point, Pa., USA. This is a new, further-attenuated, live measles virus vaccine, derived from Enders 749 D (Edmonston) vaccine, by selection through 64 passages in chick-embryo tissue-cultures, at low temperatures.

Sterile saline served as placebo for inoculating the children in the control group.

Clinical observations

Only children in good health and without fever at the time of inoculation were included. They were vaccinated in the " well-baby " clinics by teams of public health nurses.

The clinical observations were recorded 6–14 days after inoculation. Daily rectal temperature and clinical reactions were entered on the standard record cards supplied by WHO. Medical students and public health nurses were specially trained to perform the follow-up examinations; all children with severe reactions or complications, however, were examined by physicians of the respective areas, and their observations were communicated to the member of the team who was responsible for keeping the records.

Serological examinations

A total of 200 children (45% of those inoculated), selected at random, were checked for measles antibody immediately prior to the inoculation and about 30 days later. The blood was collected from finger pricks using paper rondelles. The pre- and post-inoculation sera were simultaneously examined for antibody titre using the micro haemagglutination-inhibition method. At the completion of the trial, those children whose sera contained measles antibody before inoculation were excluded from the final evaluation, so that the clinical assessment was made on a total of 421 children (Table 1). Their sex and age distribution is shown in Table 2.

TABLE 1

NUMBER OF CHILDREN INOCULATED AND CLINICALLY AND SEROLOGICALLY ASSESSED

Treatment group	Inoculated	Clinically assessed	Serologically assessed
Enders Edmonston vaccine	90	88	48
Beckenham vaccine	88	84	32
Schwarz vaccine	87	81	41
Moraten vaccine	90	84	37
Placebo	89	84	42
Total	444	421	200

RESULTS

Febrile reactions

The incidence of fever in the inoculated children is summarized in Table 3. Febrile reactions of $\geqslant 37.5°C$ in the different treatment groups varied from 86.4% in the Enders Edmonston group to 63.1% in the Moraten group and 51.2% after placebo inoculation. The numbers of children who exhibited temperatures of $\geqslant 38.3°C$ (101°F) showed even greater differences.

The mean number of days from inoculation to the onset of fever and the mean duration of fever are recorded in Table 4. Fever started about 1 day later in the children who received Enders Edmonston or Beckenham vaccines compared with those who received Schwarz or Moraten vaccines. Fever lasted longer in the Enders Edmonston group than in children in the Moraten group. No differences were found in the mean duration of maximum temperature.

Fig. 1 illustrates the incidence of temperatures $\geqslant 38.3°C$ due to each of the vaccines in the whole group of inoculated children and in the 3–<4-year and $\geqslant$4-year age-groups separately. The incidence of fever was always in the same relative order: Enders Edmonston > Beckenham > Schwarz > Moraten > Placebo.

Rash

The incidence of rash (Table 5) was greatest in the groups inoculated with Enders Edmonston and

TABLE 2

SEX AND AGE DISTRIBUTION OF CHILDREN CLINICALLY ASSESSED

Treatment group	Total no. clinically assessed	Sex		Age (months)				
		Male	Female	9–11	12–23	24–35	36–47	⩾ 48
Enders Edmonston vaccine	88	44	44	13	9	22	32	12
Beckenham vaccine	84	39	45	13	9	16	32	14
Schwarz vaccine	81	43	38	8	10	14	37	12
Moraten vaccine	84	43	41	11	10	13	38	12
Placebo	84	44	40	12	12	16	31	13
Total	421	213	208	57	50	81	170	63

TABLE 3

NUMBER OF CHILDREN DEVELOPING FEVER

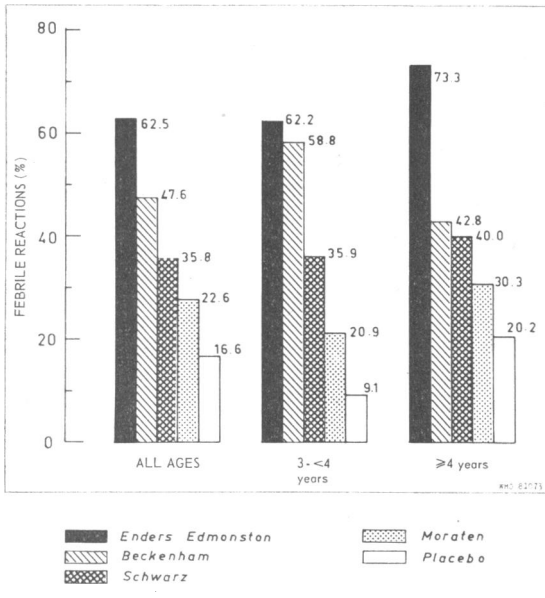
Treatment group	No. of children inoculated	Degree of fever									
		⩾ 37.5°C		⩾ 38.3°C							
		No.	%	Total		38.3°C–39.2°C		39.3°C–39.9°C		⩾ 40°C	
				No.	%	No.	%	No.	%	No.	%
Enders Edmonston vaccine	88	76	86.4	55	62.5	28	31.8	19	21.6	8	9.1
Beckenham vaccine	84	66	78.6	40	47.6	28	33.3	8	9.5	4	4.8
Schwarz vaccine	81	54	66.7	29	35.8	17	21.0	10	12.3	2	2.5
Moraten vaccine	84	53	63.1	19	22.6	14	16.7	4	4.8	1	1.2
Placebo	84	43	51.2	14	16.7	8	9.5	5	6.0	1	1.2

TABLE 4

MEAN NUMBER OF DAYS FROM INOCULATION TO ONSET OF FEVER AND MEAN DURATION OF FEVER IN INOCULATED CHILDREN

Treatment group	Mean no. of days to onset of fever	Mean duration of fever (days)	Mean duration of maximum temperature (days)
Enders Edmonston vaccine	8.2	2.8	1.0
Beckenham vaccine	8.2	2.5	1.1
Schwarz vaccine	7.6	2.4	1.3
Moraten vaccine	6.8	2.1	1.1
Placebo	8.2	2.3	1.0

FIG. 1
DISTRIBUTION OF FEBRILE REACTIONS, ⩾38.3°C, IN THE DIFFERENT TREATMENT GROUPS BY AGE-GROUP



Beckenham vaccines (36.4% and 36.9%); it was less in the group given Schwarz vaccine (28.4%) and lowest (20.2%) in those given Moraten vaccine. In the placebo group, rash was recorded in 11.9% of the children but in most cases the clinical form of the rash was mild. Only small differences were observed between the inoculated groups in the duration of the rash and the number of days to onset (Table 5).

Additional clinical phenomena

The incidence of signs and symptoms relating to the upper respiratory and digestive tracts, which have commonly been reported to follow measles vaccination, is summarized in Table 6. Table 7 summarizes the complications which immediately followed the different inoculations and lists the 4 children who required hospital admission.

Serological results

Table 8 shows the numbers of seroconversions in the 5 different groups. The proportions were 92.7% after Beckenham vaccine, 97.1% after Schwarz vaccine and 100% after Enders Edmonston and Moraten vaccines. In each of the cases of seroconversion a 4-fold or greater rise in antibody titre was observed. In addition, 3 of the 37 children given placebo reacted with high seroconversion titres. Since clinical measles was not observed in these cases, and since measles was not prevalent at the time, one possible explanation is that these children were inoculated by mistake with vaccine and misrecorded. The geometrical and arthmetical means of the antibody titres are illustrated in Fig. 2.

DISCUSSION

The trial was carried out prior to the usual increase in incidence of upper respiratory diseases associated with cold weather, and at a time when no measles outbreaks were recorded in any of the districts included in the trial. Of the 4 live measles vaccines used in the present study, 3 had been extensively tested in various countries; the fourth (Moraten) had been tested previously in only a few trials.

TABLE 5
INCIDENCE, SEVERITY AND DURATION OF RASH IN THE INOCULATED CHILDREN

Treatment group	No. of inoculated children	Incidence of rash				Mean duration of rash (days)	Mean no. of days to onset of rash
		Total		Mild	Severe		
		No.	%	No.	No.		
Enders Edmonston vaccine	88	32	36.4	30	2	2.7	9.1
Beckenham vaccine	84	31	36.9	28	3	2.4	10.0
Schwarz vaccine	81	23	28.4	22	1	2.5	9.1
Moraten vaccine	84	17	20.2	16	1	2.7	9.0
Placebo	84	10	11.9	10	—	2.4	9.1

TABLE 6

INCIDENCE OF UPPER RESPIRATORY AND DIGESTIVE PHENOMENA IN INOCULATED CHILDREN

Treatment group	Total no. of children inoculated	Upper respiratory and digestive phenomena				
		Coryza (%)	Cough (%)	Conjunctivitis (%)	Pharyngo-tonsillitis (%)	Diarrhoea (%)
Enders Edmonston vaccine	88	56.8	37.5	43.1	26.1	9.1
Beckenham vaccine	84	48.8	35.7	19.0	32.1	17.8
Schwarz vaccine	81	45.6	44.4	16.0	29.6	12.3
Moraten vaccine	84	40.4	30.9	19.0	19.0	14.2
Placebo	84	39.3	28.5	13.1	10.7	11.9

TABLE 7

IMMEDIATE COMPLICATIONS AND HOSPITAL ADMISSIONS FOLLOWING MEASLES VACCINE INOCULATION

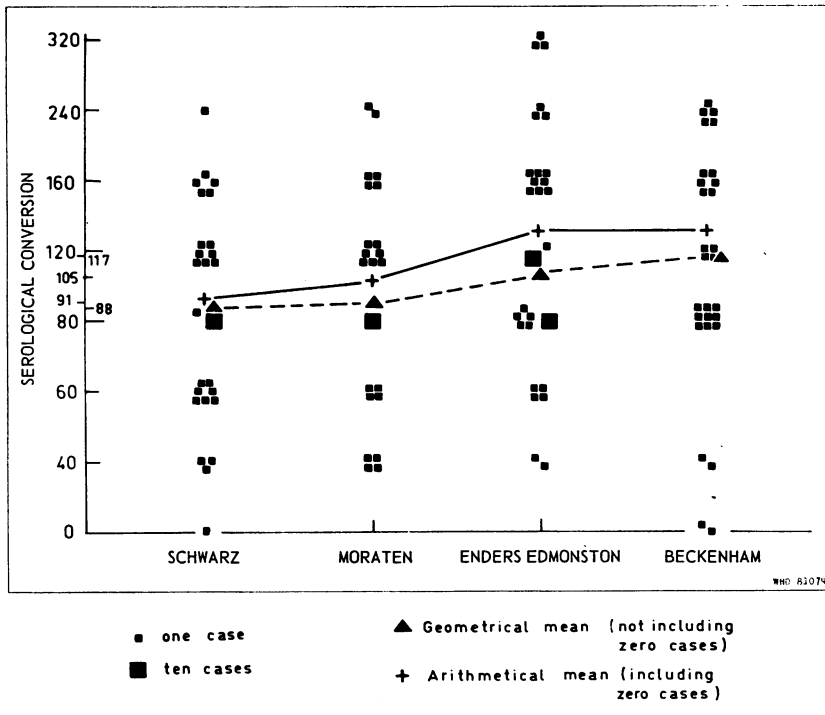
Treatment group	Total no. of complications	Otitis media	Acute diffuse bronchitis	Regional lymphadenitis	Convulsions	Hospital admissions
Enders Edmonston vaccine	4	2	2	—	—	1
Beckenham vaccine	1	1	—	—	—	1
Schwarz vaccine	2	1	—	1	—	1
Moraten vaccine	4	3	—	—	1	1
Placebo	1	—	1	—	—	—
Total	12	7	3	1	1	4

TABLE 8

SEROLOGICAL RESULTS OF THE COMPARATIVE VACCINE STUDY

Treatment group	No. of sera tested	No. positive before inoculation	No. of sera negative before inoculation									
			Total	No serological response	Serological conversion							
					Total	1:40	1:60	1:80	1:120	1:160	1:240	1:320
Enders Edmonston vaccine	48	2	46	—	46	2	4	15	11	8	3	3
Beckenham vaccine	32	4	28	2	26	2	—	9	4	6	5	—
Schwarz vaccine	41	6	35	1	34	3	7	11	7	5	1	—
Moraten vaccine	37	6	31	—	31	4	4	10	7	4	2	—
Placebo	42	5	37	34	3	—	—	—	—	2	1	—

FIG. 2
GEOMETRICAL AND ARITHMETICAL MEANS OF ANTIBODY TITRES AMONG THE VACCINATED CHILDREN



The results with 3 vaccines, Enders Edmonston, Beckenham and Schwarz, are within the range of response previously recorded by different investigators. The new, further-attenuated Moraten vaccine gave the mildest clinical reactions and also gave excellent serological results.

The 4 vaccines can be listed as follows in decreasing order of the fever ($\geqslant$37.5) induced: Enders Edmonston (86.4%), Beckenham (78.6%), Schwarz (66.7%) and Moraten (63.1%). The same decreasing trend was seen when pyrexias of $\geqslant$38.3°C and $\geqslant$40°C were considered. It should be noted, however, that such temperatures were also recorded in the placebo group, though to a lesser extent. Moraten vaccine induced very few fevers with high temperature and the numbers were comparable to those in the placebo group.

As previous authors have presented differing reports on the relation between age and the frequency and intensity of febrile reactions (Miller et al., 1967; Hutchinson, 1967; Martin du Pan, 1965) our data were analysed by age-groups. No significant differences were found between the 4 vaccines in the percentage of pyrexias $\geqslant$38.3°C occuring in the various age-groups.

The presence of rash is subject to a certain amount of subjective bias and, therefore, must be considered a less reliable sign than fever in the evaluation of reactions to the administration of live measles vaccines. The presence of a rash in 11.9% of children inoculated with placebo strengthens this opinion. It is to be noted that in our trials the frequency of rashes in the 4 inoculated groups showed the same decreasing trend as that seen for the febrile reactions, i.e., more rashes in the groups of children inoculated with Enders Edmonston and Beckenham vaccines (36.4% and 36.9% respectively) than in those given Schwarz vaccine (28.4%) or Moraten vaccine (20.2%).

The low incidence of severe reactions and complications following administration of all the measles vaccines should be stressed; only 1 case of

TABLE 9

SUMMARY OF CHARACTERISTIC CLINICAL AND SEROLOGICAL RESULTS IN CHILDREN INOCULATED WITH 4 ATTENUATED LIVE MEASLES VACCINES

Treatment group	Febrile reactions		Rash (%)	Seroconversion	
	Temperature ⩾ 38.3°C (%)	Mean duration of fever (days)		(%)	Geometric mean
Enders Edmonston vaccine	62.5	2.8	36.4	100.0	117
Beckenham vaccine	47.6	2.5	36.9	92.7	109
Schwarz vaccine	35.8	2.4	28.4	97.1	88
Moraten vaccine	22.6	2.1	20.2	100.0	91

convulsions was recorded for the whole series of 337 children. This low incidence of convulsions may have been due to the very strict selection of the children with regard to their previous history of febrile convulsions. Seven days after inoculation of measles vaccine in her left arm, one child developed a mild non-suppurative lymphadenitis of the left maxilla which cleared up quickly. No pneumonia, no encephalitis and no deaths were recorded. The 4 hospital admissions were associated with diarrhoea (2 cases), acute diffuse bronchitis (1 case) and convulsions (1 case).

All the vaccines used in the trial had a strong immunogenic effect. The results with Beckenham and Schwarz vaccines are similar to those already known from previous studies (Cockburn et al., 1966), while the 100% conversion rate registered with Enders Edmonston vaccine is greater than the rate generally reported. The conversion rate in children inoculated with the Moraten vaccine was also 100%.

A summary of the characteristic clinical and serological responses to each of the 4 vaccines used in this trial is shown in Table 9.

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RÉSUMÉ

Un groupe de 421 enfants âgés de 9 mois à 4 ans a été choisi au hasard en vue d'un essai comparatif à double insu portant sur quatre vaccins antirougeoleux atténués, à savoir: trois vaccins déjà amplement utilisés (Enders de souche Edmonston, Beckenham et Schwarz) et une nouvelle souche vaccinale plus atténuée (vaccin Moraten). Le groupe témoin a reçu du sérum physiologique.

Des réactions fébriles atteignant ou dépassant 37,5°C ont été observées chez 86,4% des enfants immunisés au moyen du vaccin Enders, 78,6% des enfants immunisés au moyen du vaccin Beckenham, 66,7% des enfants immunisés au moyen du vaccin Schwarz, 63,1% des enfants immunisés au moyen du vaccin Moraten et 51,2% des enfants témoins. Le nombre des enfants chez lesquels la pyrexie a atteint ou dépassé 38,3°C accusait des différences encore plus nettes.

La fréquence du rash dans les quatre groupes vaccinés a été respectivement la suivante: 36,4% (vaccin Enders), 36,9% (vaccin Beckenham), 28,4% (vaccin Schwarz) et 20,2% (vaccin Moraten). Aucune différence significative n'est apparue entre les différents groupes en ce qui concerne la fréquence des symptômes intéressant les voies respiratoires supérieures et de la diarrhée. Sur l'ensemble des 421 enfants, 12 seulement ont présenté d'autres réactions dont un cas de convulsions fébriles.

Les examens sérologiques ont été pratiqués sur du

sang capillaire obtenu par piqûre au doigt et recueilli sur des rondelles de papier, avant et environ 30 jours après la vaccination. On a mesuré le titre des anticorps inhibant l'hémagglutination et constaté que chacun des quatre vaccins avait un fort pouvoir immunogène: les taux de séroconversion étaient de 92,7% pour le vaccin Beckenham, de 97,1% pour le vaccin Schwarz et de 100% pour les vaccins Enders et Moraten.

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