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MEASLES VACCINES

Report of a WHO Scientific Group

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MEASLES VACCINES

Report of a WHO Scientific Group

The WHO Scientific Group on Measles Vaccine Studies met in Geneva from 15 to 20 July 1963. Dr Alvarado, Director, Division of Malaria Eradication, opened the meeting on behalf of the Director-General and welcomed the members of the Scientific Group. The purpose of the meeting, he said, was to bring together the information already available on measles vaccine; to add information obtained on more recent studies, including those sponsored by WHO; to assess the present status of measles vaccines; and to make recommendations regarding further studies and the utilization of the vaccines, especially in those developing countries where measles presents a serious problem.

INTRODUCTION

Since 1954, when Enders and his co-workers first demonstrated reliable techniques for the growth and propagation of the measles virus in tissue culture, workers in many parts of the world have been actively engaged in efforts to provide a safe and effective vaccine against the natural disease. Both live, attenuated strains of measles virus and inactivated forms of vaccine have been, and are being, developed and tested. In November 1961 the status of measles and the progress in developing measles vaccines were reviewed in an International Conference on Measles Immunization. The clear and urgent need for measles vaccination, particularly in the developing countries, was implicit in reports from these countries in which it was noted that in some of them 5% or more of children under five years of age might be expected to die from the disease. Substantial progress in the development of safe and efficacious vaccines was recorded in a number of important studies carried out chiefly in the USA and in Europe.

It was apparent that it was of considerable importance to extend the appraisal of the safety, efficacy and applicability of these vaccines to the developing countries, where the need for the vaccines was most urgent. In November 1961, therefore, WHO sought the advice of a group of experts regarding the WHO programme on measles vaccination. In accordance with their advice, studies were developed and sponsored in eight countries. In other countries collaboration and exchange of information with workers already in the field were begun.

ENDERS' EDMONSTON B STRAIN VACCINE

In 1954, Enders and his co-workers first propagated measles virus in human renal-cell cultures and later successfully developed an attenuated variant of the measles virus termed the "Edmonston strain". This attenuation was accomplished by many serial passages of the virus in human renal cells and amnion cells. The virus was subsequently introduced into developing chick embryos and, after six serial passages therein, was found to grow readily in chick-embryo cell cultures. In contradistinction to natural strains of the virus, the attenuated strain failed to cause viraemia when injected intravenously into monkeys susceptible to measles and could not be recovered from the nasopharynx or spinal fluid when inoculated intracerebrally. Inoculation of the vaccine into children susceptible to measles caused some fever in most, a rash in about half, but relatively few signs of disability or malaise. All the children developed specific measles antibodies. Susceptible children in contact with those vaccinated exhibited no clinical or serological evidence of infection.

Previously reported studies employing the Enders Edmonston vaccine

Since the initial observations, the vaccine, administered by subcutaneous injection, has been tested and evaluated in over 25 000 children in small-scale studies, mainly in the USA, and administered to over 1 500 000 children in the USA as a routine vaccination. It has also recently been given to over 700 000 children in a mass campaign in Upper Volta. In many of the trials and in the present routine vaccination in the USA a small dose of gamma globulin (40-80 measles-neutralizing antibody units per pound of body weight) has been administered concomitantly but at a different site. When the vaccine is injected without gamma globulin, about four-fifths of the susceptible children develop pyrexia, beginning about the sixth day and lasting two to five days. In 20% to 40% the rectal temperature rises to 39.5°C (103°F) or over. A modified measles-like rash develops in about half the children during the fever or shortly afterwards. Some develop Koplik's spots, cough, coryza and conjunctivitis.

When gamma globulin is administered at the same time as the vaccine, the clinical symptoms of the attenuated illness are further modified. The incidence of high fever (39°C or more) is reduced to 15%-20%, the duration of fever is curtailed, and the incidence of rash is brought down to approximately 10%-15%.

Convulsions of the febrile type, occurring five to seven days after vaccination, have seldom been reported from the USA, but several such episodes have been reported in England. However, in the USA, electroencephalograms of vaccinated children showed a slight transient abnormal-

ity in one (out of forty), compared with definite abnormalities in 50% of over 600 measles cases. The vaccinated child with the abnormal encephalogram was suffering from an intercurrent respiratory infection.

Children suffering from tuberculosis, asthma, cystic fibrosis, cardiac disease and other chronic pulmonary conditions and congenital abnormalities have been vaccinated, mostly with gamma globulin given concomitantly, without untoward effect. However, of eight children with acute leukaemia who were vaccinated with the Enders vaccine and gamma globulin, one developed a giant-cell pneumonia and died from what was concluded to be a persistent subchronic infection with the vaccine strain.

Careful studies demonstrated that varying the dose of attenuated vaccine from as little as 45 TCID₅₀ to 500 000 TCID₅₀ resulted in essentially no difference in the severity of the illness induced. The response appeared to be an all-or-none phenomenon dependent only on multiplication of the virus. This response, however, can be prevented if too large a dose of gamma globulin is administered concomitantly with the vaccine. Similarly, the successful vaccination of infants up to eight months of age may be prevented by the persistence of passive maternal antibody.

The incubation period of the attenuated disease is three to five days shorter than the natural illness, and this has suggested the possibility that vaccination at or soon after a presumed exposure to measles might block the natural infection. The few observations that have been possible suggest that protection may be afforded if the vaccine is administered on or before the day of exposure, but its effectiveness after exposure has not yet been shown.

The possibility of natural transmission of the attenuated virus from infected children to susceptible contacts has been carefully evaluated. Despite close contact of serologically susceptible institutionalized children with those experiencing symptoms of the attenuated disease, none of the susceptible group demonstrated clinical illness or evidence of serological conversion. Rarely, in fact, has it been possible to isolate virus from those vaccinated parenterally.

With the vaccine alone an antigenic response, as measured by complement-fixing and neutralizing antibodies and anti-haemagglutinins, developed about 12-15 days after vaccination in over 95% of those vaccinated. Antibody titres approached those observed after naturally acquired measles and fell in a similar way over a 6- to 12-month period, thereafter persisting at a relatively constant level. Antibody titres among those given gamma globulin concomitantly with the live vaccine did not reach as high a level initially, but after two years were similar to those observed when the vaccine was used alone.

It has been shown in field studies in which there were control groups that the vaccine, given alone or with gamma globulin, confers protection of the order of 95%-100% against natural infection. Surveillance of the

vaccinated children has revealed no indication of disappearance of immunity during a period of as long as four years among those given attenuated vaccine alone, and as long as two years in those given the live attenuated vaccine with gamma globulin. Observations are continuing.

Vaccination by methods other than injection

Vaccination with the live attenuated vaccine by methods other than injection has been attempted, with mixed success. Relatively large dosages of vaccine virus, 1500-6000 TCID₅₀, have been administered intranasally and into the conjunctival sac, applied by swabbing to the buccal mucosa, tongue, oropharynx and palate, and given as an aerosol. Intranasal administration has been accompanied by a high frequency of serological conversion in some studies but has met with relative failure in others. Aerosol application has also met with variable success in different studies. In those in whom the attenuated illness was induced the onset was later (10-15 days after administration) than among those given the vaccine by injection, and symptoms tended to be somewhat more frequent.

Recent studies employing the Enders Edmonston B vaccine

Under WHO auspices small-scale studies were recently made in Chile, India and South Africa¹ to obtain information on the reactions to Enders' Edmonston B strain vaccine and on antibody response in children in those countries. Other studies were made with this vaccine in Iceland, and a mass vaccination programme was conducted in Upper Volta.

Studies in Chile

A total of 530 children, eight months to three years of age, were included in a double-blind study (Table 1). Of the five groups into which they were divided randomly, each of about 100 children, Group I received vaccine alone; Group II, vaccine plus 0.01 ml (40 units) gamma globulin per pound of body weight; Group III, vaccine plus 0.005 ml gamma globulin; and Group IV, vaccine plus 0.0025 ml gamma globulin. Group V were controls inoculated with sterile tissue-culture medium.

During the observation period children were examined daily by a nurse, who took rectal temperatures. Children with a very high temperature or severe clinical symptoms were seen by a paediatrician.

Sex, nutritional status, and age made no difference to the postvaccinal reaction. A temperature of over 39°C (102.2°F) was observed in 26% of

¹ These investigations were supported by the World Health Organization and by United States Public Health Service Research Grant No. E-3718 (C1) to the World Health Organization.

TABLE 1. VACCINE STUDIES IN CHILE

Group	No. of children	Temperature						Rash	
		Under 38°C		38°-39°C		Over 39°C		No.	%
		No.	%	No.	%	No.	%		
I	109	39	35.8	42	38.5	28	25.7	41	37.6
II	110	53	48.2	35	31.8	22	20.0	26	23.6
III	110	54	49.1	40	36.4	16	14.5	20	18.2
IV	108	54	52.8	25	24.1	26	24.1	23	27.2
V	93	82	89.1	7	7.6	4	3.3	3	3.2

the children who received the vaccine alone. Febrile reactions usually appeared after the fifth postvaccinal day. Of the children given the vaccine alone, 38% had a rash, diffuse but mild. In children of Groups II, III and IV fever and rash were less frequent.

Other symptoms, such as coryza, cough, and pharyngitis, were very frequently observed in all five groups. Conjunctivitis, diarrhoea, and enanthemata were seen in a higher proportion of cases in the four groups that received vaccine than in the control group. Seven children had Koplik's spots, three of them in Group I. One case of convulsions was observed, associated with high temperature, in Group II.

Six months after completing the observations, children of Groups I and V were reviewed in order to determine whether any cases of measles had occurred during this period. No cases had occurred in the vaccinated group, but 14 cases, with one death from obstructive laryngitis, had occurred in the control group.

Paired blood samples were taken from children of all five groups, the first sample immediately before the vaccination, the second at the end of the observation period (28-32 days).

A good conversion from negative to positive was obtained by the complement-fixation (CF) and haemagglutination-inhibition (HAI) tests in Groups I to IV. No changes were observed in the control group.

Studies in India

In India, two separate studies were carried out comprising 92 and 316 children, respectively. The children were between eight months and three years of age. The general plan of the studies was essentially the same as in Chile.

In the smaller study, febrile reactions over 38.9°C (102°F) were observed in 17%-44% of the groups vaccinated and rash was seen in 8%-36%. The simultaneous administration of gamma globulin appeared to have no

TABLE 2. VACCINE STUDIES IN INDIA

Group	No. of subjects	Symptoms following vaccination (%)					
		Fever	Rash	Cough	Coryza	Conjunctival congestion	Convulsions
I	67	98	67	95	90	49	1.4
II	65	92	6	46	71	21	0
III	65	96	26	83	77	16	0
IV	65	98	53	96	87	32	1.4
V	54	41 ^a	2	67	31	2	0

^a Patients presented with a mild infection and had a temperature below 37.8°C (100°F).

effect on the frequency with which the clinical reactions occurred. Serological conversion, measured by the haemagglutination-inhibition test, occurred in 81 out of 87 (93%) of the children.

In the larger trial (Table 2) the varying dosages of gamma globulin again appeared to have little effect on the febrile response to immunization. Both the percentage with fever of any degree and the percentage with fever exceeding 38.9°C (102°F) were approximately the same in all the groups. Rash, cough, coryza, and conjunctival congestion occurred with somewhat less frequency among those receiving the larger doses of gamma globulin. Two children experienced convulsive episodes, one each in Groups I and IV, the former on the fourth day after vaccination and the latter on the fifth and fourteenth days. Both attacks were related to the height of the fever. There were no other signs of central nervous system involvement. Paired blood samples from the second study are shortly to be tested serologically.

Studies in South Africa

Measles vaccine was given, concomitantly with 0.25 ml gamma globulin, to four different groups of infants: in a South African National Tuberculosis Association settlement, in a hospital ward for infants with tuberculosis, and in two homes for normal children, mostly orphans. All the children were tested for immunity against measles before vaccination, and each group included children with and without neutralizing antibodies against measles.

Fever over 39.5°C (103°F) occurred in 17% of the 82 children with no previous antibody and in 5% of the 164 with previous neutralizing antibody. Rash was observed in seven of the seronegative group and in one of those who were seropositive. Other symptoms were rarely noted and did not differ significantly between the two groups.

In 63 out of 70 children (90%) serological conversion occurred.

After these small-scale studies, a mass vaccination campaign was undertaken to vaccinate all the infants between the ages of three months and three years living in the African township of Johannesburg. Measles vaccine in a dose of 0.25 ml was given at the same time as triple antigen (0.5 ml diphtheria, pertussis and tetanus) was given in the other arm. The campaign was completed within two weeks, and 22 000 children (about 75% of the total of this age-group) were vaccinated.

Subsequently the mothers of 333 infants brought them to the medical clinics because of illnesses which might have been induced by the vaccine. Most had fever, rash, cough, coryza, or conjunctivitis, but of more concern was the occurrence of convulsions in 4% of the 333 infants. However, there were no known serious sequelae to the vaccination.

Studies in Iceland

A series of studies to appraise clinical reactions and immunological responses to Enders' Edmonston B vaccine with and without gamma globulin (80 units per pound of body weight) was conducted among children and adults in Iceland. The vaccinated groups comprised 692 serologically susceptible subjects, including 384 over twenty years of age (140 of whom were over forty years of age). Control groups were simultaneously evaluated. In the principal phases of the study, all individuals were seen every two days. Rectal temperatures were taken twice daily.

The magnitude and frequency of the febrile response were somewhat less among adults than among children; so, too, was the incidence of rash. Other symptoms, such as headache, myalgia, and pain in the eyes on movement, were more frequent. Gamma globulin, simultaneously administered, reduced all the signs and symptoms significantly. The incubation period between the vaccination and the onset of symptoms varied from less than seven days in children to more than nine days in the older adults. Incubation periods of 13-14 days were not uncommon among adults.

Among those vaccinated, two cases of ill-defined paralytic illness occurred, one in a 44-year-old male who became ill on the twentieth post-vaccinal day, the second in a 16-year-old female who became ill on the fifteenth day. Both patients recovered completely. The first patient appeared to have had a vascular accident; the second had lower-extremity paralysis for one month and was considered most likely to have multiple sclerosis, although a myelitis associated with the vaccine could not be ruled out.

Of 195 persons thus far examined serologically, all except two developed antibodies following vaccination. Serological responses among adults were parallel to those in children.

Mass vaccination in Upper Volta

In late 1962 a mass vaccination programme was undertaken in Upper Volta with the Enders Edmonston B strain vaccine applied by jet injector. Approximately 730 000 children, aged six months to four years, were given vaccine. Comprehensive data are not yet available on this study, but those vaccinated are said to have been in general free from untoward reactions. Incomplete reports from a few central hospitals indicate that a number of children were admitted because of supposed complications including fever, dehydration, toxic states, convulsions, encephalitis, and gastroenteritis. Whether these were coincidental or related to the vaccine is not yet known.

FIELD TRIALS OF OTHER ATTENUATED VACCINE STRAINS

Field trials with other attenuated measles-virus vaccine strains have been conducted in Japan, Nigeria (Ilesha and Imesi), USSR, and Yugoslavia under WHO auspices¹; and in Nigeria (Ibadan) and the USA.

For purposes of comparison of clinical reactions and immunogenic effects, the trials each included both a placebo group and a group given Enders' Edmonston B vaccine or, in one study, Beckenham vaccine 4A, which is very similar to Enders' Edmonston B vaccine. Each of the trials was conducted as a double-blind evaluation, in which neither the children's parents nor the investigators appraising the reactions knew which preparation the child had received. One or more of the following vaccine strains were evaluated in the different studies:

1. *Enders' Edmonston B vaccine*: See description in preceding section, page 6.

2. *Biken vaccine* (Japan): Prepared by Dr Okuno from the supernatant of chick-embryo amniotic-membrane emulsion, this strain was derived by 61 passages of the Toyoshima strain in chick-embryo amniotic membrane.

3. *Denken vaccine* (Japan): Prepared by Dr Matumoto from bovine kidney-cell culture, this, the Sugiyama strain, was originally isolated in monkey kidney tissue culture from a patient with measles. It subsequently underwent six passages in monkey kidney tissue cultures, six in human conjunctival-cell tissue cultures, and 45 in primary bovine kidney cells at 37°C.

¹ These investigations were supported by the World Health Organization and by United States Public Health Service Research Grant No. E-3718 (C1) to the World Health Organization.

4. *Fadeeva's vaccine* (USSR): This vaccine was derived from a measles-virus variant strain, USSR 58, which was adapted to human amnion tissue cultures and subsequently to chick-embryo fibroblast tissue culture.

5. *Beckenham vaccine 4A* (UK): This vaccine is essentially Enders' Edmonston B vaccine.

6. *Beckenham vaccine 14* (UK): This vaccine was derived from Enders' Edmonston A vaccine strain which had undergone three passages through chick-embryo tissue cultures at 37°C, followed by 38 passages in chick-embryo tissue cultures at 33°C at 7-day intervals, and then by 24 passages at 4- to 5-day intervals in chick-embryo tissue cultures at 33°C.

7. *Beckenham vaccine 16* (UK): This vaccine was derived from vaccine 4A which had undergone 30 additional passages in 7- to 8-day-old chick embryos.

8. *Beckenham vaccine 20* (UK): This vaccine, a descendant of Enders' Edmonston B primary seed virus, has been subjected to a total of 71 additional chick-embryo tissue culture passages at 33°C.

9. *Milovanović's vaccine* (Yugoslavia): Prepared by the limiting dilution method, this strain represents the 94th passage of Enders' Edmonston B strain in chick-embryo tissue culture.

10. *Schwarz's vaccine* (USA): This vaccine, a descendant of Enders' Edmonston A strain, has undergone 77 additional passages in chick-embryo tissue culture.

11. *Smorodincev's vaccine* (USSR): The Leningrad-4 strain was originally isolated in human renal-cell cultures and subsequently underwent 26 passages in human renal-cell tissue cultures and 35 in primary human amnion-cell cultures. It was adapted to chick-embryo cell cultures. The vaccine was prepared from material obtained after 9-15 passages in diploid guinea-pig renal-cell tissue cultures.

Studies in Yugoslavia (Milovanović's vaccine)

Comparative evaluation of Enders' Edmonston B vaccine and Milovanović's vaccine both with and without gamma globulin (40 units per pound of body weight) was carried out in Belgrade in December 1962 (Table 3). The field trial included 202 children of eight months to three years of age. All the children were seen twice daily between the fifth and fifteenth days and rectal temperatures were taken twice daily.

The frequency of fevers (39.5°C and over) was found to be essentially the same among all the vaccinated groups, although the duration of the

TABLE 3. VACCINE STUDIES IN YUGOSLAVIA

Vaccine:	Enders' Edmonston B	Enders' + gamma globulin	Milovanović's	Milovanović's + gamma globulin	Placebo
No. in group:	41	40	41	41	39
Temperature ^a (% distribution):					
Under 38.0°C	24	33	37	54	85
38.0°-39.4°C	59	55	49	36	13
39.5°C and over	17	12	14	10	2
Mean duration (days)	4.0	3.8	2.5	2.1	1.1
Other symptoms (% distribution):					
Rash	46	25	20	22	2
Cough	54	57	57	52	49
Coryza	56	52	60	70	56
Conjunctivitis	49	27	35	17	15
Diarrhoea	17	32	12	22	5
Tonsillitis-pharyngitis	29	17	17	10	2
Antibody response:					
Serological conversion (HAI)	26/27	26/26	26/27	29/29	1/29
Geometric mean HAI titre (reciprocals)	415	303	303	304	—
Convulsions (number of cases)	2	0	0	0	0

^a Rectal.

febrile response was shorter among those receiving Milovanović's vaccine. A rash was observed in almost half of those receiving Enders' vaccine alone and in one-quarter to one-fifth of those in the remaining three vaccine groups. Follicular tonsillitis was observed in 10%-29% of children in each of the vaccinated groups but in only one child in the control group. The tonsillitis was associated with an increased febrile response but was otherwise asymptomatic. Bacteriological culture of throat swabs obtained from many of these children revealed no significant associated pathogens. Other symptoms were approximately equally distributed among all the groups, including those receiving the placebo preparation. Two of the children who received Enders' vaccine without gamma globulin had convulsions on the second day of a marked febrile response.

Serological conversions, as measured by the haemagglutination-inhibition test, approached 100%; geometric mean titres were, however, somewhat higher among those who received Enders' vaccine without gamma globulin.

Studies in Japan (Biken and Denken vaccines)

Between October 1962 and July 1963, comparative studies of Denken and Biken vaccines and Enders' Edmonston B vaccine, each given with and without gamma globulin, were carried out simultaneously in 20 centres in different parts of Japan (Table 4). Included were 1723 children between six months and five years of age with no previous history of measles. A total of 504 served as placebo controls for the various vaccines given.

Enders' and Denken vaccines were injected subcutaneously; Biken vaccine was administered intranasally by a nebulizer over a one-minute period. Gamma globulin, when administered, was given subcutaneously in a dose of 0.01 ml (40 units) per pound of body weight. Following vaccination, the children were examined daily by a paediatrician, and temperatures were taken four times a day.

TABLE 4. VACCINE STUDIES IN JAPAN

Vaccine:	Enders' Edmonston B	Enders' Edmonston B + gamma globulin	Denken	Denken + gamma globulin	Biken	Biken + gamma globulin	Placebo
No. in group ^a :	174	170	185	179	142	126	462
Temperature (% distribution):							
Under 38.0°C	8	20	10	23	3	13	81
38.0°-38.9°C	18	35	36	48	23	37	15
39.0°C and over	74	45	54	29	74	50	4
Mean duration (days)	3.7	2.5	3.2	2.5	4.5	2.9	—
Other symptoms (% distribution):							
Rash	64	39	83	64	65	47	4
Cough	59	58	57	62	74	67	48
Coryza	34	29	31	31	32	33	23
Conjunctivitis	33	32	39	28	44	29	14
Diarrhoea	33	34	37	32	49	36	27
Vomiting	1	2	2	2	1	2	1
Antibody response:							
Serological conversion (CF)	174/191	170/192	185/200	179/196	142/206	126/186	16/478
Geometric mean CF titre (reciprocals)	49	37	39	32	60	52	< 4
Convulsions (number of cases)	4	3	4	2	3	2	0

^a The numbers shown for the vaccinated groups include only those showing CF response of $< \frac{1}{4}$ - $\geq \frac{1}{4}$ after vaccination. The placebo group excludes those showing seroconversion.

Of the 1723 children originally selected for study, 74 (4%) were excluded because of pre-existing complement-fixing antibodies at or above a titre of 1:4. Serological conversions, measured by complement-fixation test (CF), to a titre of 1:4 or greater were observed in approximately 90% of those receiving Enders' and Denken vaccines but in only 68%-69% of those receiving Biken vaccine. The relative failure of response to Biken vaccine was attributed to technical failures in the use of the nebulizer apparatus in some clinics.

Reactions following vaccination in those in whom serological conversion took place revealed a somewhat greater frequency of pyrexia over 39°C among those receiving Enders' vaccine than among those receiving Denken vaccine. A rash occurred more frequently among those who received Denken vaccine; other symptoms appeared with about equal frequency in the two groups.

The Biken and Enders' vaccine groups did not differ so far as the incidence of high fever or rash was concerned. But (though not shown in the table) the mean day of onset of fever was about three days later in the Biken than in the Enders group. As shown in the table, the fever lasted longer in the Biken group. Convulsions occurred in all groups except the controls. Gamma globulin mitigated the frequency of high fever and the incidence of rash in all groups.

Studies with Smorodincev's vaccine in the USSR

In the USSR, Enders' Edmonston B vaccine and Smorodincev's vaccine were evaluated with and without gamma globulin in a series of controlled trials in children's institutions (Table 5). Gamma globulin was administered in a dosage of 40 units (0.01 ml) per pound of body weight with Enders' vaccine and in a total dosage of 0.6 ml with Smorodincev's vaccine. The children were examined daily by paediatricians and axillary temperatures recorded twice daily.

Fever over 38°C (axillary) and other signs and symptoms except rash occurred more frequently following administration of Smorodincev's vaccine than following administration of Enders' vaccine. The occurrence of rash was slightly less when the Smorodincev vaccine was used. Gamma globulin completely eliminated severe constitutional symptoms and considerably diminished the proportion of high febrile reactions, the frequency of rash, and many of the other associated symptoms.

High specific antibody responses occurred in 95% of the vaccinated children.

Large-scale field trials of the efficacy of the Smorodincev vaccine were initiated late in 1961 in Leningrad and subsequently extended to other regions of the USSR (Table 6). Over 500 000 children between one and eight years of age in nurseries, kindergartens, and schools were included.

in the trials. Vaccine was administered concomitantly with 0.5 ml gamma globulin, and a proportion of the children in each institution were left unvaccinated to serve as controls. Outbreaks of measles have occurred thus far in 307 of the institutions. As shown in the table, a significant degree of protection has been observed in all areas.

TABLE 5. STUDIES WITH SMORODINCEV'S VACCINE IN THE USSR

Vaccine:	Enders' Edmonston B	Enders' + gamma globulin	Placebo	Smorodincev's	Smorodincev's + gamma globulin	Placebo
No. in group:	90	90	180	90	90	180
Temperature ^a (% distribution):						
Under 37.0°C	47	74	89	23	56	78
37.0°-38.0°C	24	13	3	34	22	12
Over 38.0°C	29	13	8	43	22	10
Other symptoms (% distribution):						
Rash	28	14	4	20	5	1
Cough	28	21	8	77	33	27
Coryza	35	18	3	80	44	32
Conjunctivitis	20	16	8	40	33	12
Tonsillitis-pharyngitis	59	42	15	75	36	27
Vomiting	4	5	0	32	0	0

^a Axillary.

TABLE 6. PROTECTIVE EFFECT OF SMORODINCEV'S VACCINE WITH GAMMA GLOBULIN

Cities and Republics	Number of children's institutions with outbreaks	Vaccinated children			Children not vaccinated			Coefficient of effectiveness
		Number of contacts	Became ill		Number of contacts	Became ill		
			No.	%		No.	%	
Kirghizia	49	1045	18	1.7	1820	538	29.6	17.5
Kaliningrad	21	359	9	2.5	564	242	42.9	17.1
Lucansk	63	1192	21	1.8	1723	489	28.4	15.7
Leningrad	42	1066	24	2.2	2247	663	29.5	13.4
Sverdlovsk	12	153	6	3.9	195	89	45.6	11.7
Azerbaijan	120	2455	34	1.4	2124	584	27.5	19.6
Total	307	7270	112	1.5	8673	2605	30.2	

Studies with Fadeeva's vaccine in the USSR

Fadeeva's vaccine, derived from the weakly reactogenic strain USSR 58, has also been evaluated in controlled trials both with and without gamma globulin (Table 7). The vaccine was given subcutaneously in a dosage of 1000 TCID₅₀. Febrile response, rash and other signs and symptoms did not differ significantly from the placebo group. After a single injection of the vaccine 70% of the children vaccinated developed specific antibodies; after two injections 80%; and after three, 90%. The average neutralization antibody titre after two injections was 1:104, and after three injections 1:160.

TABLE 7. PROTECTIVE EFFECT OF FADEEVA'S VACCINE

Group	Number of children	Illness not contracted, %	Illness contracted, %	Course of measles			
				Miti-gated, %	Mild, %	Typical, average severity	
						Without compli-cations, %	With compli-cations, %
3 injections of vaccine	11 000	70.2	29.8	19.9	5.0	4.5	0.6
2 injections of vaccine	5 699	32.0	68.0	20.0	20.0	20.0	8.0
Non-vaccinated controls:							
Gamma globulin given	6 000	35.0	65.0	35.0	15.0	12.0	3.0
No gamma globulin given							

In 1958, studies of the protection afforded by Fadeeva's vaccine were initiated in nurseries among children aged six months to three years. Outbreaks have since occurred in each of these nurseries. The protection afforded by three injections of the vaccine was 70% during this five-year period.

Studies in Nigeria (Beckenham vaccines)

In April 1963 trials were conducted in Ibadan to compare the relative reactogenicity of three strains of attenuated measles vaccines developed in the United Kingdom. These were Beckenham vaccine 4A, comparable to Enders' Edmonston B vaccine, and two further attenuated strains, Beckenham vaccine 16 and Beckenham vaccine 20. Children between

TABLE 8. VACCINE STUDIES IN IBADAN (NIGERIA)

Vaccine :	Beckenham 4A	Beckenham 16	Beckenham 20	Placebo
No. in group :	17	38	24	34
Temperature ^a (% distribution) :				
Under 100°F (37.8°C)	23	16	8	41
100°-102.8°F (37.8-39.4°C)	65	66	92	50
103°F (39.5°C) and over	12	18	0	9
Mean duration (days)	2.5	2.7	1.8	0.9
Other symptoms (% distribution) :				
Rash	35	50	17	3
Cough	53	60	50	62
Coryza	41	74	54	56
Conjunctivitis	6	2.5	0	3
Tonsillitis-pharyngitis	18	42	12	21
Diarrhoea	41	45	29	50
Vomiting	0	16	17	12
Convulsions (number of cases)	0	1	0	0

^a Rectal.

the ages of six and eighteen months, many of whom were undernourished, took part. All children not on routine antimalarial therapy were given a curative dose of chloroquine at the beginning of the trial and a weekly dose of pyrimethamine thereafter. The children were examined daily by physicians and rectal temperatures obtained.

Though the number of children in each of the comparison groups was small, the results indicated that most of the signs and symptoms following vaccination were least pronounced and the duration of fever shortest following administration of Beckenham vaccine 20 (Table 8).

In another group of 360 children, a further appraisal of Beckenham vaccine 20 was subsequently undertaken, utilizing for comparative purposes a control group given inactivated poliomyelitis vaccine (Table 9). The children were examined once between the fourth and sixth day after vaccination, daily from the eighth to the twelfth day inclusive, and on the fifteenth and twenty-first day. Rectal temperatures were recorded at the time of examination. Blood specimens were obtained from one-third of the children. After exclusion of those known to be serologically immune and those who were not regularly examined in the clinic, 137 of the vaccine group and 57 in the control group remained for evaluation.

The frequency of febrile responses and rash was somewhat higher in the vaccinated than in the control group; other symptoms were not markedly different in frequency in the two groups.

TABLE 9. FURTHER VACCINE STUDIES IN IBADAN (NIGERIA)

Vaccine:	Beckenham 20	Placebo
No. in group:	137	57
Temperature ^a (% distribution):		
Under 100°F (37.8°C)	27	42
100°-102.9°F (37.8-39.4°C)	63	53
103°F (39.5°C) and over	10	5
Mean duration (days)	2.5	1.6
Other symptoms (% distribution):		
Rash	11	5
Cough	59	67
Coryza	59	51
Conjunctivitis	4	2
Diarrhoea	31	24
Tonsillitis-pharyngitis	39	40
Vomiting	7	5
Convulsions (number of cases)	1	0

^a Rectal.

Nine cases of naturally acquired measles developed soon after vaccination in the vaccine group and two among the controls. One convulsive episode occurred in an 11-month-old vaccinated infant during an illness that had been characterized by some diarrhoea and vomiting prior to vaccination, followed by coma on the seventh postvaccinal day and subsequent death; the evidence at autopsy suggested a non-bacterial encephalitis. This case is still under study.

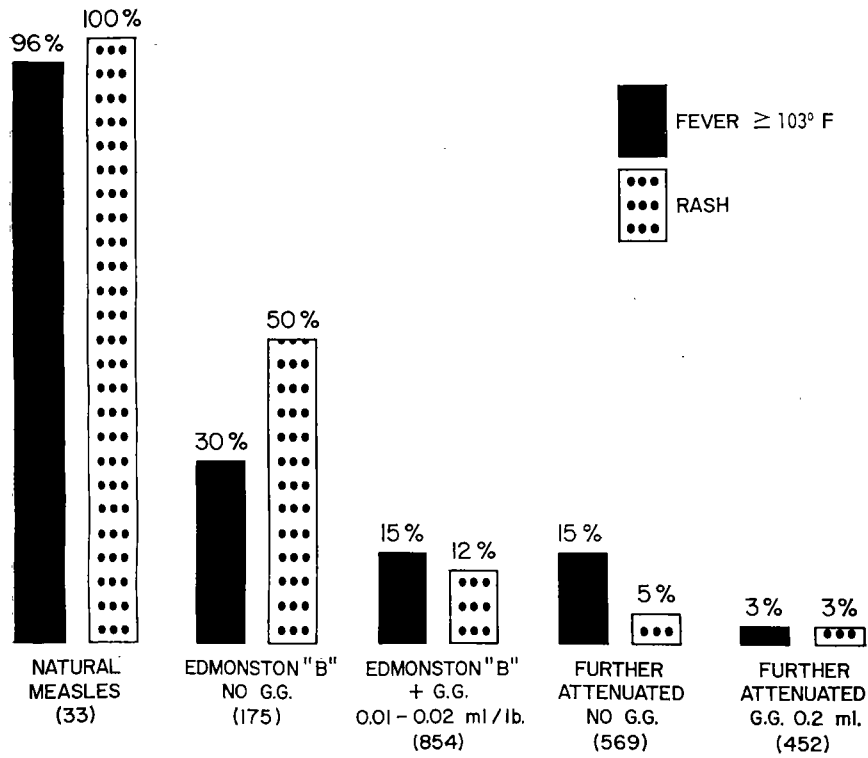
In 51 of 55 children without prevaccination antibody there was a fourfold or greater rise of neutralizing antibody titre after vaccination.

Studies of Schwarz's vaccine in the USA and Nigeria

Comparative studies of Schwarz's further attenuated vaccine with Enders' Edmonston B strain have been carried out in the USA and in Ilesha and Imesi, Nigeria.

The principal studies in the USA were conducted among both institutionalized and home-dwelling children with no prevaccination antibodies to measles. They ranged in age from one to eight years. Gamma globulin was administered to all receiving Enders' vaccine and to some who received Schwarz's vaccine, initially in a dosage of 40 units per pound of body weight, subsequently in a dose of approximately 8 units per pound. The institutionalized children were under close daily observation by physicians. Parents of children living at home recorded rectal temperatures once or twice daily and rash and other reactions for 14-18 days after vaccination.

FIG. 1. PERCENTAGE INCIDENCE OF FEVER AND RASH FOLLOWING NATURAL MEASLES INFECTION AND VACCINATION



Numbers in parentheses indicate total number of susceptibles evaluated.

Reproduced with permission from Krugman, S., Giles, Joan P., Jacobs, A. Milton & Friedman, Harriet (1963) Pediatrics, 31, 919.

Data from some of these studies are shown in Fig. 1. The frequency of febrile responses exceeding 103°F (39.5°C) was approximately 15% both for those receiving Schwarz's vaccine and for those given Enders' vaccine with gamma globulin. The occurrence of rash was less than half as frequent among those receiving Schwarz's vaccine. Administration of gamma globulin with Schwarz's vaccine brought both the febrile response and the occurrence of rash down to negligible levels.

The immunological response, as measured by the haemagglutination-inhibition test, exceeded 97% in all the vaccinated groups. The persistence of antibodies for as long as two years following administration of Enders' vaccine with gamma globulin and for one year following administration of Schwarz's vaccine is depicted in Fig. 2 (from an unpublished study by J. P. Giles et al.).

FIG. 2. MEASLES HAEMAGGLUTINATION-INHIBITION ANTIBODY RESPONSE AND PERSISTENCE FOLLOWING NATURAL INFECTION AND VACCINATION

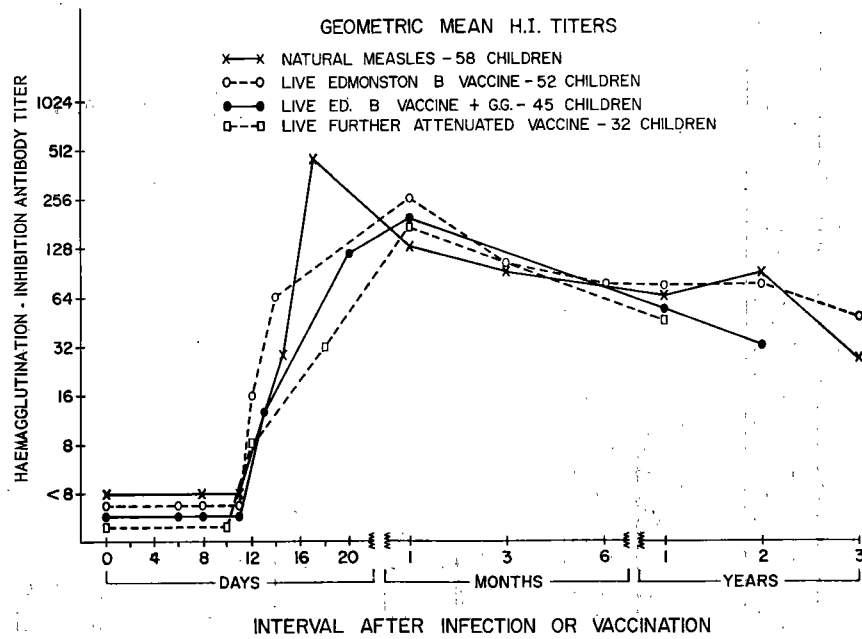


TABLE 10. VACCINE STUDIES IN ILESHA AND IMESI (NIGERIA)

Vaccine:	Enders' + gamma globulin	Schwarz's	Placebo
No. in group:	102	108	149
Temperature ^a (% distribution):			
Under 100°F (37.8°C)	35	39	70
100°-102.8°F (37.8-39.4°C)	56	56	27
103°F (39.5°C) and over	9	5	3
Other symptoms (% distribution):			
Rash	9	10	1
Cough	74	60	58
Coryza	29	36	33
Conjunctivitis	2	4	0
Diarrhoea	32	40	29
Vomiting	2	1	0
Convulsions (number of cases)	2	1	0

^a Rectal.

In the trials in Ilesha and Imesi, Nigeria (Table 10), groups given Schwarz's vaccine were compared with those given a placebo or Enders' vaccine with gamma globulin (40 units per pound of body weight). Children between eight months and three years of age were included. Those who arrived for vaccination with high fever or other symptoms had their vaccination postponed; all others were included. The children were examined once daily by a paediatrician from the sixth to the twelfth day inclusive after vaccination; rectal temperatures were taken at the time of examination. Blood specimens were obtained from every fifth child.

Fever of 103°F (39.5°C) or over was somewhat more frequent among those receiving Schwarz's vaccine than among the controls and less frequent than among those receiving Enders' vaccine with gamma globulin. Other signs and symptoms, including rash, revealed few differences between the two vaccinated groups. Two of those receiving Enders' vaccine and one of those given Schwarz's vaccine developed convulsions.

An antibody response, as measured by haemagglutination-inhibition, occurred in the 13 serologically susceptible children who received Enders' vaccine and in the 18 susceptibles who received Schwarz's vaccine.

SEVERE REACTIONS FOLLOWING VACCINATION

Vaccine studies reported to the Group included many in areas where serious childhood illnesses are common. The reactions, therefore, necessarily have to be evaluated in terms of signs and symptoms manifested by control groups. Isolated episodes of serious illness were, in this context, particularly difficult to appraise.

The only regularly encountered severe reaction in all trials with unmodified Enders' Edmonston B vaccine was a high temperature. It reached 39.5°C (103°F) or over in about one-quarter of those vaccinated (Table 11) and occasionally reached 40.5°C (105°F) or over. There is no evidence that this febrile response caused any lasting harm directly, but it may occasionally have delayed recognition of intercurrent disease.

TABLE 11. SEVERE FEBRILE REACTIONS TO VACCINE IN SIX COUNTRIES

Group	No. of persons studied	Temperature 39.5°C (103°F) and over	
		No.	%
Enders' Edmonston B vaccine	905	222	24.0
Enders' Edmonston B vaccine + gamma globulin	961	141	15.0
Control	240	11	4.6

Various other severe reactions have sometimes occurred. The commonest of these are convulsive attacks. Data on this reaction from 14 different carefully controlled studies in 10 countries are summarized in Table 12. In these trials most of the subjects were under three years of age and the results are probably not typical for other age-groups. The convulsions occurred most frequently in infants and appear to have been a consequence of fever and not of specific involvement of the central nervous system by measles virus. The reports of convulsions were usually based on information supplied by parents and may not always have been accurate.

TABLE 12. CONVULSIONS IN VACCINATED AND CONTROL GROUPS
IN 14 STUDIES

Group	No. of persons studied	Convulsions	
		No. of cases	%
Enders' Edmonston B vaccine	1201	25	2.1
Enders' Edmonston B vaccine + gamma globulin	2646	17	0.6
Further attenuated strains	490	1	0.2
Controls	1957	3	0.15

Other central nervous system reactions, as manifested by a variety of clinical syndromes, have been noted occasionally. Five cases of "encephalitis" have been reported in a total of 160 000 vaccinated in controlled trials. Clinical and pathological details of these cases are not available, nor is the rate for coincidental encephalitis among the non-vaccinated known. One fatal case of encephalitis occurred in a vaccinated child in a controlled study. Symptoms began on the sixth postvaccinal day, but the central nervous system changes and autopsy findings were not indicative of measles encephalitis. One case of paraplegia with urinary retention occurred in a 16-year-old, the onset being on the fifteenth postvaccinal day, with recovery after one month. Detailed studies indicate the probable diagnosis to be multiple sclerosis, but the possibility of myelitis due to measles vaccine cannot be excluded. One case of diplopia, one of diplopia with ataxia, and one of simple cerebellar ataxia have also been reported within four weeks of vaccination. The significance of these single cases cannot be evaluated at this time.

Follicular tonsillitis or exudative pharyngitis has been seen in four studies, the incidence rates being up to 15% above the rates in the controls. The occurrence of this condition has been sporadic and, except for associated increased fever, relatively asymptomatic. Bacteriological cultures from these cases have rarely yielded pathogenic organisms.

Bronchitis and pneumonia have been noted, but the incidence of these conditions among those vaccinated has not significantly exceeded the rates in control groups. One fatal case of staphylococcal pneumonia, confirmed at autopsy, began on the fifth day after vaccination and thus cannot be related to the vaccine:

In some trials a slightly increased incidence of diarrhoea has been observed in those vaccinated, but this was not associated with increased morbidity. The one death reported associated with diarrhoea after vaccination occurred too early to be reasonably attributable to the vaccine.

INACTIVATED MEASLES VACCINE

Concentrated, formol-inactivated, alum-precipitated Edmonston strain virus vaccine has been prepared in monkey kidney and chick-fibroblast cell cultures. It is stable at refrigerator temperatures for at least 12 months.

Reactions to the vaccine are comparable to those which accompany injection of other alum-containing vaccines such as DPT (diphtheria and tetanus toxoids and pertussis vaccine).

Antibody responses are related to dosage and to the age of the recipient. Infants under six months of age rarely respond and, when they do, only to low titres. In older persons with pre-existing measles antibody there is a booster effect in approximately 60%. One or two doses of vaccine induce seroconversion in less than 50% of children. Three doses of 0.5 ml inactivated vaccine administered at 2- to 4-week intervals will stimulate measles antibody in approximately 90%. Mean titres 4-6 weeks after vaccination are somewhat lower than those induced either by natural measles or by Enders' live vaccine. Antibodies gradually decline over a period of 6-12 months and may be undetectable after one year.

Protective efficacy as measured in field trials

Initial small-scale trials of the inactivated vaccine were initiated late in 1960 and extended to more extensive double-blind, placebo-controlled trials in 1961 in several communities in the USA.

The inactivated vaccine was administered in these trials in either a two- or three-dose schedule of 0.5 ml or 1.0 ml vaccine given subcutaneously. The interval between injections was commonly 30 days, although during an epidemic a second dose administered 7 days after the first and a third dose 21 days later provided substantial protection.

During the first six months following immunization, vaccine efficacy, as measured by the occurrence of cases of measles of all degrees of severity in the different studies, was consistently 80%-88%; protection against cases of typical measles was 92%-95%. The preliminary data from one

study in which controlled observations were possible 12-18 months after vaccination showed that the efficacy of the vaccine had declined to 65% for all reported measles cases and 75% for cases of typical measles.

Unlike those vaccinated with the live vaccine, which appears to block subsequent infection by the wild virus, many who have received the inactivated vaccine have developed infection in contact with the natural disease. Infection has ranged from the subclinical to, in a few cases, typical measles. Substantial boosts in antibody titres have followed such infection. The illness observed among vaccinated children has frequently been mild and of short duration; febrile responses have been variable but generally low; the rash, when seen, has often been atypical in distribution and transient; and associated symptoms have commonly been minimal.

COMBINATIONS OF INACTIVATED AND LIVE VACCINE

Live vaccine administered 1-6 months after one or two doses of inactivated measles vaccine has been shown to evoke a marked increase in antibody titre. In studies conducted in the USA and the USSR, the clinical reactions normally induced by the live vaccines prepared from the Enders and the Smorodincev strains were reduced and were similar to those which follow the most highly attenuated live vaccine strains.

Less than 10% of those vaccinated in this way had a temperature over 103°F (39.5°C). Rashes and other clinical signs and symptoms were infrequent. After administration of the killed vaccine, modification of the clinical signs and symptoms induced by the administration of live vaccine is usually apparent for at least six months whether or not there has been a decline in the antibody titre induced by the killed vaccine.

Preliminary results from a continuing large-scale, carefully controlled field study in the USA indicate that this combination confers a protective efficacy of at least 95% for 18 months following administration. A large-scale study to determine the degree of protection afforded is in progress in the USSR.

COMBINED USE OF MEASLES VACCINE AND OTHER ANTIGENS

The large number of infectious diseases against which protection can be afforded in early life makes it desirable, if not imperative, that combined vaccines be sought for the purpose of simplifying administration and reducing to a minimum the number of visits to the physician. To be acceptable such combined vaccines must provide adequate immunologic response to all components and must be safe. The latter consideration is of special importance where live virus vaccines are being combined.

Inactivated vaccine

Inactivated measles-virus vaccine has been combined with inactivated trivalent poliovirus vaccine in an alum formulation. With certain lots of vaccine of adequate potency, patients given three doses of vaccine one month apart showed antibody responses to combined vaccine which were similar to those obtained when the individual vaccines were given alone.

A combination of inactivated measles vaccine with DPT might be of value. Pertussis vaccine ought to be given early in life, starting at one or two months of age, if deaths are to be prevented. At this early age the immunologic response to inactivated measles vaccine may be very poor because of a basic immunologic unresponsiveness, combined with a suppressive effect brought about by the presence of maternal measles antibody. It remains to be determined whether children so vaccinated will give a booster-type response to an injection given some months later.

Live vaccine

Live measles-virus vaccine has been given in combination with smallpox vaccine and also with smallpox and 17D yellow fever-virus vaccines by means of the jet injector. Limited studies in about 200 children were carried out in Upper Volta in persons of low socio-economic condition. The antibody responses to the measles and yellow fever components and the smallpox "takes" were reported by the investigator to be essentially the same in the combination form as when the vaccines were given independently. The reported clinical reactions to the polyvalent vaccines were said not to be appreciably greater than when the individual components were given alone. It is realized, however, that the reactions to the vaccine may have been obscured by other simultaneous infections. Certainly further studies of this sort should be encouraged, to develop simple, practicable and safe means for simultaneous immunization against a variety of diseases.

CONTRA-INDICATIONS TO USE OF MEASLES VACCINES**Inactivated vaccines**

Vaccine prepared in egg should not be given to egg-sensitive persons. Apart from this there appear to be no contra-indications to the use of inactivated measles vaccine. The theoretical possibility of sensitization to monkey kidney tissue has not been confirmed by any report to date. The generally accepted principle that vaccination procedures should not be undertaken in the course of severe febrile illness except in special circumstances applies to the use of inactivated measles vaccines.

Live measles vaccine

On theoretical grounds there are a number of conditions in which administration of live measles vaccine would appear to be contra-indicated. These include :

1. Pregnancy
2. Leukaemia, lymphoma and other general malignancies
3. Therapy which depresses resistance, such as steroids, irradiation, alkylating agents and antimetabolites
4. Acute severe febrile disease
5. Severe active tuberculosis
6. Severe protein malnutrition (kwashiorkor)
7. Severe chronic respiratory-tract infections

It is apparent, however, that individuals who fall into any of the categories listed may be those at greatest risk and most in need of protection from natural measles. If the use of inactivated vaccine is precluded because of unavailability or lack of time, interim passive protection can be provided with gamma globulin. In certain circumstances, use of the live attenuated vaccine either alone or with gamma globulin might be preferable to allowing the natural disease to occur.

There is no evidence at present to show that the use of live measles vaccine in early pregnancy is associated with foetal abnormalities, but on general grounds the use of live vaccines, particularly during the first trimester, should be avoided if possible.

Live measles vaccines should not be administered within six weeks after the administration of gamma globulin or to infants under eight months of age, since in these circumstances circulating measles antibody may prevent successful vaccination.

PRECAUTIONS IN USE OF LIVE ATTENUATED MEASLES VACCINES**Storage**

Aqueous live measles virus is best stored frozen in sealed glass vials at -70°C in Dry Ice or a mechanical refrigerator.

The freeze-dried products so far developed generally contain less than 2% residual moisture. Such vaccines are generally stable at room temperature for about two weeks, but at 37°C for only a few days. They are stable indefinitely when stored at -20°C or below, and may be stored in the refrigerator at $+4^{\circ}\text{C}$ for at least one year.

Particular care must be exercised in the shipping of live virus vaccines, since untoward conditions may be encountered en route. Much the safest

procedure is to ship with an adequate amount of Dry Ice or with chemical refrigerants and to check the condition of the refrigerants on arrival of the material at the destination. Once rehydrated, measles vaccine is stable for eight hours when held in the refrigerator at $+4^{\circ}\text{C}$. If unused after eight hours it should be discarded.

Administration

Measles virus belongs to the myxovirus family, members of which contain essential lipid in their structure and are extremely sensitive to destruction by many substances such as alcohols, surface-active agents, acids, etc. It is therefore important that distilled water used for reconstituting dried virus should be pure and free of preservatives. Such water must, of necessity, be dispensed in sealed glass ampoules.

The syringes used either for rehydrating the virus or for vaccine administration must be clean and rinsed free of detergents used for washing them and must not be boiled in water in which syringes used to give other vaccines have been or are being boiled, since harmful preservatives may be present. By far the best procedure is to use sterile plastic disposable syringes and discard them after using them only once.

Even a very small amount of gamma globulin contains sufficient measles antibody to neutralize the virus in the vaccine. Measles vaccine and gamma globulin must not, therefore, be given in the same syringe, nor must the same syringe be used first for gamma globulin and afterwards for the vaccine. The vaccine and gamma globulin must be injected at different anatomical sites.

THE LARGE-SCALE USE OF VACCINES

The information collected in the past five years on measles vaccines represents strenuous efforts in many countries by laboratory and field workers who have carried out numerous small-scale and some large-scale field trials. Many health administrations are now facing the question of whether or not to set up at this stage large-scale community vaccination programmes.

The indications for mass vaccination depend on the one hand on the importance of the disease in the country concerned and, on the other, on the safety, efficacy, acceptability, availability, cost and ease of administration of the vaccine.

Importance of the disease

Reports have recently been made of high death rates from measles in young children in densely populated parts of the world in which birth

rates are high, malnutrition, malaria, tuberculosis and gastro-enteritis common, and medical services limited. In such countries there is a strong case for prevention of the disease as quickly as possible. In other countries, where the number of deaths even in epidemic years is very low, the importance of the disease is to be measured by the incidence of encephalitis and its sequelae, by the incidence of severe respiratory complications, and by the social and economic consequences of an illness from which practically no child escapes.

There is little *precise* information on the importance of measles either in developing or in developed countries. This information must be obtained and carefully evaluated in relation to the advantages and disadvantages of the vaccines at present available before a decision on large-scale use of vaccines is made. Accurate surveys (which, if properly planned, need not be large) of morbidity and mortality in different age-groups, of complications and of the importance of associated factors such as malnutrition should therefore be set up in developing countries, and steps should be taken to ascertain the incidence and severity of encephalitis and other serious complications in developed countries.

Characteristics, advantages and disadvantages of the vaccines

Live and inactivated vaccines are available and have been shown to prevent disease. Although a satisfactory antibody response is induced by three doses of the inactivated vaccine, the protection afforded appears to decline substantially with time. The need for three doses at monthly intervals makes these vaccines unsuitable for use on a mass scale in most countries at present. If the difficulties of adding them to mixed antigens such as DPT (diphtheria/pertussis/tetanus) can be overcome, they may be useful in some countries in the future.

Of the live vaccines, several have already been sufficiently evaluated to be seriously considered for mass programmes. The advantages are ease of administration and the virtual certainty of a high degree of protection for a substantial period. The chief disadvantage is the severity of the clinical reaction: 30% of children given Enders' Edmonston B vaccine and 5%-15% of children given the further-attenuated vaccines, such as the Schwarz vaccine, have pyrexia of 103°F (39.5°C) or over for two or three days during the period of reaction. With vaccine of the Enders Edmonston B type and, to a lesser extent, with the further-attenuated vaccines, there is also a possibility of the occurrence of convulsions in a small percentage of children. There is, however, a virtual absence after vaccination of otitis media, pneumonia and encephalitis, which are common complications of the natural disease.

The use of gamma globulin to minimize reactions is not possible in most mass campaigns, particularly in developing countries. The admin-

istration of killed vaccine followed by live vaccine may be a suitable alternative to the use of gamma globulin.

The only live vaccines at present available in large quantity have characteristics similar to the Enders Edmonston B vaccine. The Schwarz vaccine may become available in the near future, as may other vaccines from well-attenuated strains. The cost of vaccines at present is considerable but is likely to fall in a few years.

Any decision to employ the present live vaccines on a large scale should be accompanied by plans for step-by-step progression, so that the number vaccinated at any one time is not too large. This is essential for a number of reasons :

1. It is still necessary that the vaccinated children should be carefully followed up so that more precise information on the nature, severity, incidence and long-term effects of reactions and untoward sequelae can be obtained ;

2. It is essential that health workers should become fully acquainted with and parents should be made fully aware of the symptoms and signs of the vaccine-induced illness which will occur ;

3. Unless the number vaccinated at one point of time is strictly limited, the medical services will be overwhelmed with requests for advice and treatment of the sick children.

Vaccines are not likely to be available in quantities sufficient to meet all needs for a considerable time. The supplies which are available should be so used as to obtain not only information on the reaction rates (as suggested above) but also information on the duration of immunity and on the effectiveness of community as distinct from individual protection. Such information can be obtained by suitable planning without adding materially to the cost of programmes and to the work of the staff concerned, and the opportunity of obtaining it over the next few years should not be lost.

REQUIREMENTS FOR VACCINE

Before vaccines are released for general use, standards for control of safety and potency will have to be set up. Where gamma globulin is to be administered along with the vaccine in order to increase the degree of modification of reactions, standards for the measles-antibody content of the gamma globulin will also be required.

Inactivated vaccine

The standards should aim at ensuring not only adequate immunizing potency as measured in tests in animals but also freedom from viable

agents. Additionally the standards should seek, through use of healthy selected animals and by appropriate tests in animals and in cell cultures, to preclude the presence of extraneous microbiological agents in the live-virus pool prior to inactivation. Special attention should be given to the exclusion of the animal oncogenic viruses, particularly SV₄₀ virus, and the avian leucosis viruses. Penicillin should not be used in the production process.

For culture, primary cells from chick embryo or monkey kidney are acceptable.

For the effective control of potency, a reference vaccine should be included in each potency test and a monospecific reference serum for virus identification made available. The safety and immunogenicity of the early batches of vaccine should be ascertained by clinical and serological studies in susceptible human subjects.

Live vaccine

Standards should aim to ensure maintenance of proper attenuation of the virulence of the virus in the vaccine and to guarantee an adequate level of infectivity as measured in tests in appropriate cell cultures. The standards should also seek, through use of eggs from "disease-free" chicken flocks and by appropriate tests in animals and in cell cultures, to preclude the presence of extraneous microbiological agents in the vaccine. Attention should be given to excluding viruses of the avian leucosis complex. Clinical safety and immunogenicity should be proved for early lots of vaccine, and penicillin should not be used in vaccine manufacture. The moisture content of the final dried product should be below a prescribed level, and the product should be stable for a minimum prescribed period of time.

Primary cell cultures from chick embryos are acceptable as culture cells. Canine renal-cell cultures and human and animal diploid-cell cultures are being considered.

A reference virus preparation is required for the control of virus titre, and a monospecific reference serum for virus identification. A reference preparation of gamma globulin is required in tests for standardization of the antibody level of gamma globulin if this is to be administered with the vaccine.

The need to ensure that both live and inactivated measles-virus vaccines for experimental and for general use are free from recognizable viable oncogenic viruses is emphasized by recent work on the avian leucosis group of viruses and on SV₄₀ virus, a member of the papovavirus group. Avian lymphomatosis virus, as measured by the RIF (resistance-inducing factor) test, has been shown to be commonly present in embryonated hens' eggs in the USA, and the existence of the disease in various parts of the world

suggests a ubiquitous distribution. Certain strains of Rous' sarcoma virus, a member of the avian leucosis complex, may induce malignant growths in rats, hamsters, guinea-pigs, mice and *Macaca* monkeys. SV₄₀ virus, commonly present in renal-cell cultures of *Macaca* monkeys, induces malignant growths in hamsters and *Mastomys* and transformation in a variety of human embryonic and adult cells in culture.

At present, eggs free from avian leucosis viruses are not readily obtainable in the quantities required for vaccine production. Until adequate supplies are available (probably within 6-18 months) countries in which measles is a serious cause of death may be faced with deciding whether the risk of injecting material that may contain live avian leucosis viruses is greater than the risks from measles. Though, as stated above, tumours have been induced in baby monkeys by the injection of avian leucosis viruses, there is no evidence of tumour induction in man. Live yellow fever vaccine (which is liable to contamination with these viruses) has been used, mainly in persons over one year of age, for many years without untoward effects being observed.

FURTHER INDICATED STUDIES

Live measles vaccine

1. Continuing search for a more attenuated yet highly immunogenic measles-virus strain is important. Though the initial studies of certain of the more attenuated strains are encouraging, a proportion of those who are given even these more attenuated vaccines develop marked febrile and other reactions. The development of a highly immunogenic vaccine giving slight reactions and conferring durable immunity with a single injection remains an important objective.

Candidate attenuated strains should be subjected to field tests, which should include a double-blind placebo-controlled field trial incorporating a reference vaccine. The reference presently recommended is the Enders Edmonston B vaccine administered with gamma globulin (40 units per pound of body weight). Not less than 100 serologically susceptible children should be included in each test group. Children should be observed at least once daily during the period of expected reactions; temperatures, preferably rectal, should be taken preferably in the late afternoon or evening, when they are likely to be at their highest. Suspicious central nervous system manifestations or unusually severe reactions should be carefully studied and reported fully. Prevacinal and postvaccinal blood specimens should be obtained from an adequate sample of the group.

Before an attenuated strain is accepted for further investigation, studies must have shown that the attenuated strain provoked substantially less

severe and less frequent febrile and other reactions than the reference strain; and serological conversions should exceed 90%, measured by the complement-fixation test, or 95%, measured by the haemagglutination-inhibition or neutralization test.

Double-blind controlled studies should then be established to measure the degree and duration of protection against natural challenge.

2. Presently available further attenuated strains, such as the Schwarz, the Milovanović and the Beckenham 20 vaccines, should be further appraised by well-controlled comparative studies as soon as possible, particularly in developing countries. Additional information is required on the following points:

- (a) the clinical response following vaccination, particularly the severity of fever, rash, respiratory symptoms, diarrhoea and any unusual severe reactions, especially those involving the central nervous system;
- (b) the durability of immunity as measured by antibody persistence and, most important, by protection against the naturally occurring disease;
- (c) the possible influence of seasonal factors on the frequency and severity of reactions.

3. Certain special problems that may result from the use of live measles vaccine deserve further elucidation:

- (a) follicular tonsillitis, which, in some limited studies, appears to be associated with an increased severity of clinical reactions: a bacterial role in the etiology of this condition has not been elucidated;
- (b) possible anergy to tuberculosis: limited studies indicate that anergy does not follow live measles vaccination, but this should be examined in more detail;
- (c) the incidence and severity of diarrhoeal disease due to recognized bacterial pathogens after large-scale live-measles-vaccine administration: notable outbreaks of diarrhoea have been observed following epidemics due to natural infection;
- (d) the effect of live measles vaccine on children suffering from malaria in highly endemic areas and on children suffering from malnutrition, with special attention to kwashiorkor;
- (e) the use of live measles vaccine in susceptible adult populations.

Inactivated measles vaccine

1. The usefulness of inactivated vaccine and of inactivated/live vaccine combinations should be appraised in leukaemic children, in patients receiving cortisone therapy, and in children with tuberculosis.

2. The durability of antibody and the duration of protective effect afforded by inactivated vaccine and inactivated/live vaccine in combination should be determined.

3. The long-term effectiveness of inactivated vaccine used alone should be investigated, both in areas where the wild measles virus is constantly or intermittently present and where it is absent.

4. A study should be made to determine whether infants who receive inactivated vaccine in the first six months of life are so protected that they do not manifest the usual clinical symptoms when given live vaccine at one year of age or later.

Combined vaccines

The safety and efficacy of combinations of the principal inactivated and live vaccines should be carefully studied. Possible antigens which might be combined include live measles vaccine, oral poliomyelitis vaccine, smallpox vaccine, yellow fever vaccine, and BCG, and such inactivated vaccines as those for diphtheria, pertussis, tetanus, measles and poliomyelitis.

SUMMARY AND CONCLUSIONS

Measles is an important disease throughout the world. There is a clear and urgent need for effective protection, especially in areas with high death rates from the disease.

Since 1958, live attenuated and inactivated measles vaccines have been under active study in many parts of the world.

The Enders Edmonston B live vaccine has been the most extensively tested. Though it uniformly confers a high order of protection following a single parenteral vaccination, use of the vaccine has been followed by high fever and rash in a significant proportion of those vaccinated. For the most part respiratory symptoms and the usual toxic manifestations associated with natural measles have been minimal. In most studies these manifestations have been substantially reduced by the simultaneous administration of gamma globulin without impairing the immunogenic effect. Infection induced by the vaccine virus does not spread by natural routes to susceptible children.

Recent controlled studies conducted under WHO auspices in Chile, India and South Africa demonstrate clinical reactions, immunogenic response and protection following use of the live vaccine similar to those observed in previous studies in the USA and the USSR.

Recent field trials in Yugoslavia, Japan, the USSR, Nigeria and the USA have appraised several additional attenuated measles-vaccine strains.

Currently available data regarding the various live attenuated strains indicate that the Smorodincev, Denken and Biken vaccines induce febrile reactions and other symptoms about as frequently as the Enders Edmonston B vaccine. Causing significantly less clinical reaction, but apparently equally immunogenic, is the Schwarz vaccine. Beckenham 20 vaccine and the Milovanović vaccine also appear promising in this respect in the light of the limited trials reported. These vaccines are given without gamma globulin. The Fadeeva vaccine, although inducing few reactions, was associated with a markedly diminished immunogenicity.

In the studies reported to the Group, significant reactions except for high fever were uncommon. Occasional convulsive episodes among vaccinated children were reported in a number of the trials; they appeared to be associated with high fevers. Isolated instances of other central nervous system illnesses following vaccination were reported, but they appeared to assume no consistent clinical pattern and could well have represented incidental occurrences unrelated to vaccination.

Inactivated, concentrated and precipitated vaccines are being extensively tested. No severe clinical reactions appear to follow their use. A significant antibody response occurs in over 90% of those given three injections. Antibody titres fall off over a 6- to 12-month period and, in many, may be undetectable by the end of that time. Preliminary results indicate a decrease in protective efficacy against "typical" measles from over 90% as observed during the initial 6-month period after vaccination to approximately 75% 12-18 months after vaccination. Many so vaccinated have been observed to develop mild or subclinical cases of measles with subsequent substantial boosts in antibody titre.

When one or two doses of the inactivated vaccine are given prior to administration of the live vaccine, clinical reactions to the live vaccine are markedly reduced and serological responses are only slightly modified. Preliminary results of the protective efficacy of this vaccine indicate that it continues at a level of 95% or better for at least 18 months.

It would be useful to be able to combine a number of inactivated and live immunizing agents. Limited studies describing results of combined vaccine administration were reported and, although encouraging, indicated the need for further study.

Various contra-indications to the use of inactivated and live vaccines were summarized and discussed.

Large-scale use of measles vaccine at this time should be undertaken only after careful thought and preparation, and then only in a progressive step-wise fashion.

Requirements for vaccine production should be based on standards ensuring a safe, potent, and effective product. Special cognizance should be taken of the potential presence of extraneous viruses, particularly the SV₄₀, avian leucosis and other oncogenic viruses.

RECOMMENDATIONS

The Group recommended that of the future studies mentioned above, special attention should be given to :

- (a) the search for further-attenuated strains which give high antibody levels and very low reaction rates ;
- (b) the setting up, in countries with different socio-economic and environmental conditions, of field trials (which should include placebo groups) to make direct comparisons of the antigenicity and reaction rates of the present further-attenuated strains. These trials should also include a group given one injection of inactivated vaccine followed by one injection of an attenuated live vaccine, such as Enders' Edmonston B, Smorodincev's Leningrad-4, or the Japanese Biken and Denken strains. The inclusion of a reference vaccine is essential.

The Group recommended that the World Health Organization should give these studies substantial financial support and should prepare detailed plans for carrying out the field studies.

The Group also recommended that the Organization should :

- (a) advise and assist countries about to use vaccine on a large scale in the planning of campaigns, so that the maximum amount of information on the safety and efficacy of the vaccine will be obtained in the next few years ;
- (b) encourage countries in developing and developed areas to set up, before they plan vaccination campaigns, epidemiological studies to determine the importance of measles ;
- (c) consider the formulation of minimum requirements for measles vaccines and the provision of the necessary standard reagents ;
- (d) investigate the possibility of earmarking supplies of vaccine (and gamma globulin if necessary) to meet emergency situations.

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