A Field Evaluation

Inactivated Measles-Virus Vaccine

W. H. FOEGE, M.D., O. S. LELAND, M.D., C. S. MOLLOHAN, M.D., V. A. FULGINITI, M.D., D. A. HENDERSON, M.D., and C. H. KEMPE, M.D.

PREVIOUS REPORTS have confirmed the safety and effectiveness of live attenuated measles-virus vaccine (*1–5*). Not only have reactions been mild, when used in conjunction with immune globulin, but the live vaccine has been effective enough to elicit an antibody response in approximately 98 percent of children who are seronegative for measles. In addition, antibody levels are detectable for periods exceeding 1 year and immunity is close to 100 percent when confronted with a measles epidemic, at least for 1 year following immunization.

Less information has been available on inactivated measles-virus vaccine. Therefore, the study reported here was designed to evaluate the protective effect of inactivated vaccine on kindergarten children exposed to measles. Also presented is the probability of subclinical infections from natural measles virus following immunization with this vaccine.

Materials and Methods

Vaccine and vaccine schedule. A formalin-inactivated, alum-precipitated, concentrated measles-virus vaccine (Edmonston strain) was used (*6* and *A*). A control group received a placebo containing the adjuvant material.

At the time of the first injection, vaccine A (measles vaccine) or vaccine B (placebo) was randomly assigned to each child. Children given vaccine A received three 1.0-ml. injections of measles vaccine at monthly intervals during the first weeks of October, November, and December 1961. Those given vaccine B received identical amounts of placebo during the same time schedule. Parents were not told which material their child received until 19 months after the study began, when measles vaccine became available commercially.

Clinical subjects. Colorado Springs, Colo., had not had a major outbreak of measles since 1956; therefore, it was anticipated that a large number of kindergarten children would be susceptible to the illness in 1961–62. Cooperation was sought from parents of the 1,900 kindergarten children in 24 elementary schools, and 480 children with no previous history of measles were enrolled in the trials. Of these children, 427 actually completed the entire series of three injections; 232 received the vaccine and 195 the placebo. At the time of the first injection all children were between the ages of 4 years, 9 months and 5 years, 9 months.

Surveillance. Surveillance of illness in both groups was maintained by school nurses who investigated any school absence of more than 4 days. In addition, all parents were asked to report by telephone any illness even remotely

Dr. Foege and Dr. Leland were formerly assigned to the Colorado State Department of Public Health from the Communicable Disease Center, Public Health Service. Dr. Foege is now at Harvard University School of Public Health and Dr. Leland is resident in cardiology at Harvard. Dr. Mollohan is chief of the epidemiology section, Colorado Health Department. Dr. Fulginiti is with the department of pediatrics, University of Colorado School of Medicine. Dr. Henderson is chief, Surveillance Section, Epidemiology Branch, Communicable Disease Center. Dr. Kempe is chairman, department of pediatrics, University of Colorado Medical Center.

The El Paso County Health Department, under the direction of Dr. M. F. Schafer, provided technical assistance in contacting children and maintaining surveillance throughout the study period.

Table 1. Final diagnosis of illnesses among 111 children participating in measles vaccine field trials, December 1961–December 1962

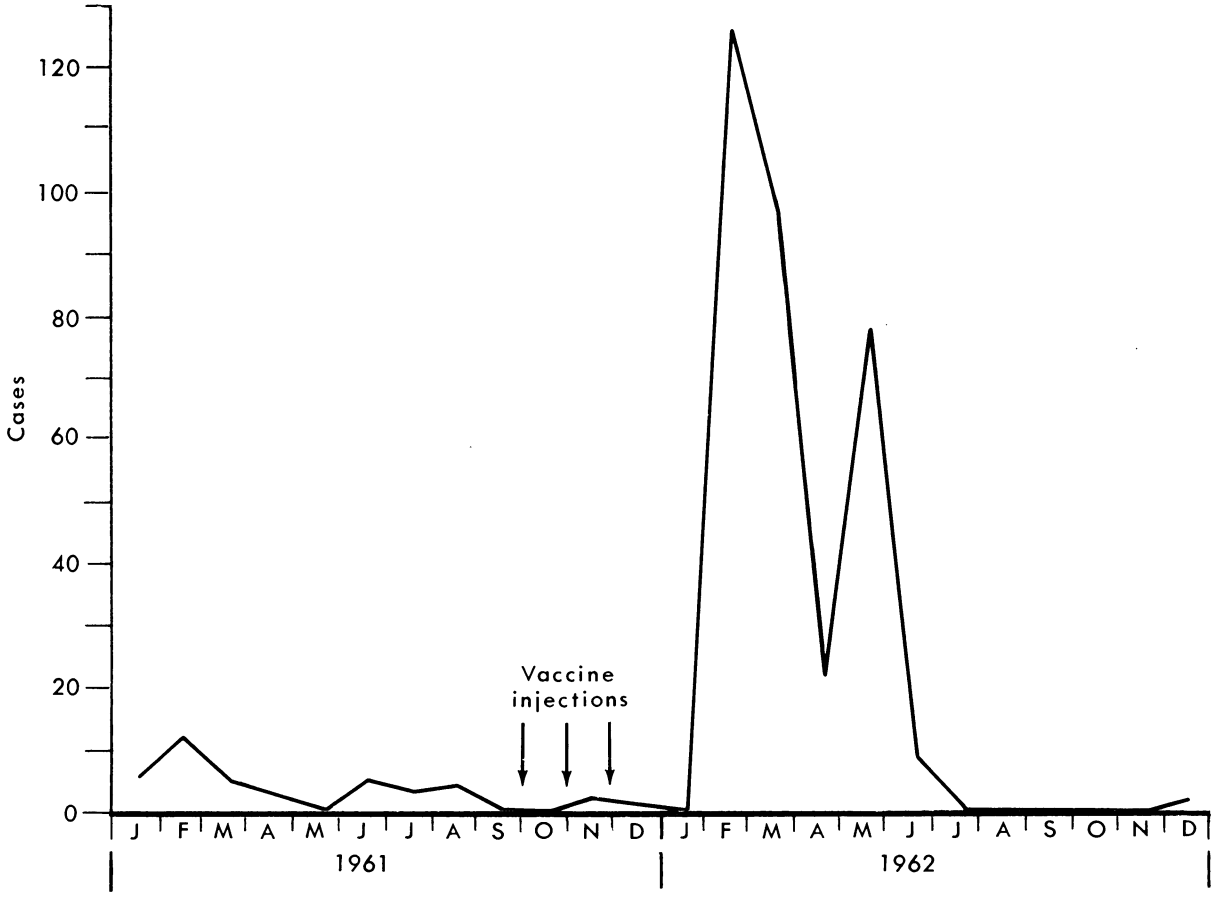
Diagnosis	Received vaccine	Received placebo
Regular measles	4	53
Mild measles	10	19
Not measles	4	3
Unknown diagnosis	10	8
Total illnesses	28	83

resembling measles. Finally, in June 1962 and again 1 year after completion of injections, questionnaires were sent to parents of the subjects asking for information on the presence or absence of measles during the study period, whether the child had been exposed to measles, and the type of exposure.

Reported cases were investigated individually by home visits or by telephone and were classified in one of four categories on the basis of the clinical course. Illness classified as regular measles had to meet the following criteria: a rash on the head, neck, and trunk for a minimum of 3 days and a temperature on at least one occasion of 103° F. orally or 104° F. rectally. When temperatures were not taken, not recalled, or did not reach these levels, the presence of fever for 4 or more days was accepted as an adequate substitute for the fever criterion. Children with measles characterized by cough or coryza, fever, and rash but not meeting the above criteria for both fever and rash, were classified as having mild measles. Illness clearly inconsistent with measles was classified as "not measles" and remaining illnesses were classified as "unknown diagnosis."

Serology. Paired serums from 18 children who received the measles vaccine were tested.

Reported cases of measles, by month, El Paso County, Colo., 1961–62



The first specimen was collected when the first vaccine dose was administered; the second specimen was obtained 6 weeks after the third and final injection. A third serum specimen was obtained from 14 of the children 10 months after the final dose.

All serums were tested by Dr. Vincent Fulginiti, using a modified hemagglutination-inhibition method as originally described by Rosen (*7, 8*).

Results

One year after completion of vaccine and placebo administration, followup information was obtained for 170 (75 percent) of the 232 children who received three injections of measles vaccine and 158 (82 percent) of the 195 children who received three injections of placebo.

An outbreak of measles in El Paso County, Colo., beginning in late January 1962, 7 weeks after the final vaccine injection, provided an ideal opportunity to test the vaccine under epidemic conditions (see graph). Of the 328 children with known histories 1 year after immunization, 111 reported illness possibly due to measles. Twenty-eight children were in the vaccine group and 83 were in the placebo group. Four children in the vaccine group met the criteria for regular measles, and an additional 10 had mild measles (table 1). Four children reported illnesses definitely not due to measles while 10 illnesses could not be diagnosed with certainty. In the placebo group, 53 children met the criteria for regular measles, 19 had mild measles, 3 had illnesses not due to measles, and for 8 a definite diagnosis could not be made.

Table 2. Number and percentage of children with regular or mild measles participating in measles vaccine field trials, December 1961–December 1962

Diagnosis	Received vaccine (170 children)		Received placebo (158 children)	
	Number	Percent	Number	Percent
Regular measles	4	2. 4	53	33. 5
Mild measles	10	5. 9	19	12. 0
Total	14	8. 3	72	45. 5

NOTE: Vaccine effectiveness

$$= \frac{(\text{Expected cases} - \text{observed cases}) \times 100}{\text{Expected cases}}$$

$$= \frac{(.455 \times 170) - 14}{.455 \times 170}(100) = 82 \text{ percent effective.}$$

Table 3. Hemagglutination-inhibition titers of 14 children before and after receiving inactivated measles-virus vaccine

Subject No.	Prevaccine (Oct. 5, 1961)	Postvaccine (Jan. 17, 1962)	Postvaccine (Oct. 8, 1962)	Measles history	Exposure history
1	<10	80	10	No	No.
2	<10	20	<10	No	No.
3	<10	80	20	No	No.
4	<10	40	<10	No	No.
5	<10	20	<10	No	No.
6	<10	80	<10	No	To playmate.
7	<10	20	<10	No	Do.
8	<10	80	40	Mild, April 1962	Home exposure.
9	<10	160	160	[1]	[1].
10	<10	40	80	Regular, April 1962.	No.
11	<10	20	80	No	Home exposure.
12	<10	40	160	[2]	Do.
13	<10	80	>320	No	Do.
14	<10	10	40	Mild, June 1962	No.

[1] Information not available.

[2] Cough, coryza, conjunctivitis, and temperature of 104.3° F. orally, in May 1962. Developed no rash.

The number and percentage of cases of regular or mild measles in both the vaccine and placebo groups are shown in table 2. The incidence of measles in the placebo group was more than five times as great as in the vaccine group. Also, the majority of children who received the placebo and had measles, had regular measles; among the vaccine-treated children who developed measles, the majority had mild measles.

Hemagglutination-inhibition titers in 3 of 18 children who received vaccine were high before immunization, indicating prior immunity despite the negative histories. All 15 seronegative children developed increased titers following measles vaccination. A third titer, 10 months after completion of immunization, was obtained in 14 of the 15 children having negative titers before vaccine administration. The titers as well as information on measles or exposure to measles are shown in table 3.

Subject No. 12 (table 3), developed cough, coryza, conjunctivitis, and a temperature of 104.3° F. orally for 3 days in May 1962. Although she developed no evidence of a rash, it is possible that her illness represented an infection with measles virus. One week after the onset of her illness two of her siblings developed regular measles. Subjects 8, 10, and 14 developed clinical measles while subjects 11 and 13 were exposed to siblings with regular measles but developed no clinical symptoms themselves.

Information from parents disclosed that 27 children who had received vaccine had been exposed to measles by ill siblings. Three such children developed regular measles and two developed mild measles. Other types of exposure, in school, playground, and so forth, were encountered by 49 children in the vaccine group; 1 developed regular measles and 3 developed mild measles.

Home exposure was reported for 15 children in the placebo group; 5 developed regular measles and 2 mild measles. Of 46 children in the placebo group who were exposed outside the home, 15 developed regular measles and 3 developed mild measles.

Comment

We are aware of the hazards of a retrospective diagnosis of measles. However, the experience of Guinee in the Cooperative Measles Vaccine Field Trial conducted in five cities (*9*) has indicated a high degree of reliability in comparing results from different investigators when measles was diagnosed on the basis of fever, rash, and days in bed.

That surveillance was for a limited period of time and therefore cannot provide answers regarding long-term vaccine protection does not detract from the validity of protection figures for the period of study.

There was a marked difference in measles incidence between the vaccine and placebo groups, and the majority of measles cases following the vaccine were mild though most cases were regular in the placebo group.

The effectiveness of the vaccine in preventing any clinical evidence of measles was:

$$E=\frac{\text{Expected cases}-\text{observed cases}\times 100}{\text{Expected cases}}$$

$$=\frac{(77.4-14)\ (100)}{77.4}=82 \text{ percent effective}$$

(table 2). The effectiveness in preventing regular measles is even more impressive, being $\frac{100\times(57-4)}{(57)}=93$ percent effective. To reemphasize, although histories were collected for 1 year following immunization, the children were not exposed to measles during the last 6 months of the year (see graph). Therefore, effectiveness figures actually pertain to the first 6 months following vaccine administration.

The effectiveness of vaccine in this group is consistent with reports of seroconversion following inactivated measles vaccine in 90 to 100 percent of susceptible children (*8, 10–12*). The effectiveness in preventing regular measles and mild measles is almost identical with the findings of the Cooperative Measles Vaccine Field Trial conducted by the Communicable Disease Center (*9*).

The decline in antibodies 10 months following immunization in children without known exposure to natural measles is as expected (*10*). Interestingly, in six children with persistently high titers 10 months after receiving vaccine, a history of either clinical measles or close exposure was always obtained, indicating the possibility of an infection with the natural virus. Information on illness or exposure was not available on a seventh child with a persistently

high titer. On the other hand, a similar history of close exposure or clinical measles could not be obtained in children with low or undetectable titers. The only known exposures in the latter group were at the playground in two instances, but never at home. It appears, therefore, that persisting antibody titers 10 months following inactivated measles vaccine could reflect a clinical or subclinical infection with the natural virus rather than a prolonged vaccine effect. If this is true, permanent immunity would not be expected from the vaccine alone. Because antibody determinations were obtained for only a small number of children, the results are indicative and not proof of these conclusions.

Summary

A placebo-controlled study of inactivated measles vaccine was conducted among susceptible kindergarten children. A community outbreak of measles between 2 and 6 months following immunization showed the vaccine to be 82 percent effective in preventing any evidence of measles and 93 percent effective in preventing regular measles. No conclusions can be drawn regarding effectiveness of the vaccine for longer periods of time.

Epidemiologic investigation and a limited number of antibody determinations suggest that persistent antibody titers 10 months following immunization are related to clinical or subclinical infections with natural measles virus rather than a prolonged effect of the inactivated vaccine. If this is true, permanent immunity would not be expected from inactivated vaccine alone.

REFERENCES

(*1*) Stokes, J., et al.: Persistent immunity following Enders live, attenuated measles-virus vaccine given with human immune globulin. New Eng J Med 267: 222 (1962).

(*2*) Hilleman, M. R., et al.: Studies of live attenuated measles virus vaccine in man. II. Appraisal of efficacy. Amer J Public Health 52: 44 (1962).

(*3*) Krugman, S., Giles, J. P., Jacobs, A. M., and Friedman, H.: Studies with live attenuated measles-virus vaccine. Amer J Dis Child 103: 183 (1962).

(*4*) Reilly, C., et al.: Living attenuated measles-virus vaccine in early infancy. New Eng J Med 26: 165–169 (1961).

(*5*) Stokes, J., et al.: Studies of live attenuated measles virus vaccine in man. I. Clinical aspects. Amer J Public Health 52: 29 (1962).

(*6*) Warren, J., and Gallian, M. J.: Concentrated inactivated measles-virus vaccine. Amer J Dis Child 103: 418 (1962).

(*7*) Rosen, L.: Hemagglutination and hemagglutination-inhibition with measles virus. Virology 13: 319 (1961).

(*8*) Fulginiti, V. A., Leland, O. S., and Kempe, C. H.: Evaluation of measles immunization methods. Amer J Dis Child 105: 5 (1963).

(*9*) Guinee, V. F., et al.: A collaborative study of measles vaccines in five United States communities. Amer J Public Health 53: 645 (1963).

(*10*) Carter, C. H., et al.: Serologic response of children to inactivated measles vaccine. JAMA 179: 848 (1962).

(*11*) Karelitz, S., et al.: Inactivated measles virus vaccine. JAMA 184: 673 (1963).

(*12*) Winkelstein, W., et al.: Inactivated measles virus vaccine. III. A field trial in young school children. JAMA 179: 398 (1962).

SUPPLY REFERENCE

(*A*) Inactivated measles-virus vaccine (Edmonston strain): Dr. Joel Warren, Chas. Pfizer & Co., Inc.