A study is reported on the use of killed vaccine, and killed plus live vaccine to protect school children against measles. Killed-live vaccine evoked higher hemagglutination inhibition titers. Study population is being kept under surveillance to obtain further information.

A COLLABORATIVE STUDY OF MEASLES VACCINES IN FIVE UNITED STATES COMMUNITIES

PRELIMINARY REPORT

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FROM THE original Edmonston strain of measles virus two types of vaccines have been developed, an attenuated live vaccine and a killed vaccine.[1,2] The live vaccine, although highly effective[3-6] and able to evoke a sustained antibody response,[4,5,7] induces significant fever and rash in a proportion of children to whom the vaccine is given.[8-11] The killed vaccine, known to confer protection against measles for at least several months after its administration,[12,13] is only accompanied by minor reactions similar in incidence and severity to those observed following commonly used alum-precipitated vaccines.[12-15] However, measles antibody titers resulting from killed vaccine are relatively transient and may drop to undetectable levels within six months after vaccine administration.[14,16]

Sequential administration of killed measles vaccine followed by live vaccine one month later revealed, in small scale trials,[15] that those given this regimen responded with antibody titers equivalent to those given the live vaccine alone. However, the frequency of rash and fever following administration of the live vaccine was markedly reduced.

To determine, under the circumstances of natural challenge, the long-term efficacy of killed vaccine and the serial combination of killed and live measles vaccine, a field trial was undertaken. Investigators in Buffalo and Rochester, N. Y., Cincinnati, Ohio, Atlanta, Ga., and Seattle, Wash., have joined with the staff of the Communicable Disease Center in conducting this study. Reported here are the results of the first year's experience.

Method

A total of 5,210 children, in the kindergarten, first, and second grades with no previous history of measles were enlisted in the study. Approximately equal numbers were included in each of the five study areas. Schools in the middle and upper socioeconomic areas of each community were selected, since previous studies have indicated that these schools would have the highest

* Names of the co-authors who participated in the study are listed at the end of this paper.

Table 1—Cooperative Measles Vaccine Field Trial Schedule of Injections and Blood Sampling

Month	Vaccination Schedule by Treatment Groups				Bleeding Schedule
	I	II	III	IV	
December, 1961	K	P	K	P	*
January, 1962	K	P	K	P	
February, 1962	K	P	L	P	
March, 1962					*
October, 1962					*
June, 1963					*

K—Killed Vaccine
L—Live Vaccine
P—Placebo
Inactivated Measles Vaccine supplied by Chas. Pfizer and Company, Inc.
Lyophilized Live Measles Vaccine supplied by Lederle Laboratories.

proportion of children with a negative measles history.

As shown in Table 1, two vaccine schedules were used: (1) a series of three injections of 0.5 ml of killed measles vaccine,* and (2) a series of two injections of 0.5 ml of killed vaccine, followed by 0.5 ml of a $10^{3.5}$TCID 50/ml preparation of live measles vaccine.† In each instance the interval between injections was approximately four weeks. Concurrently each of the two placebo groups received injections simulating the vaccines. Both the vaccines and placebos were designated by code letters only. The code designation was unknown to the investigators in each area. The four treatment groups were assigned randomly through the entire population.

Blood samples were obtained from a random 10 per cent sample of vaccinees.

* Provided by Chas. Pfizer and Company.
† Provided by Lederle Laboratories.

Table 2—Cooperative Measles Vaccine Field Trial Study Population According to Age and Prevaccination HAI Antibody Status

Population Characteristics	Treatment Group			
	KKK	PPP	KKL	PPP
Number in group	1,214	1,210	1,196	1,178
Mean age	5.65	5.65	5.63	5.65
Kindergarten	575	565	564	548
First grade	551	564	549	548
Second grade	88	81	83	82
White male	570	574	577	544
White female	534	527	512	521
Nonwhite male	53	52	52	58
Nonwhite female	57	57	55	55
Number of prevaccination blood specimens obtained	156	156	165	138
Per cent with negative HAI prevaccination blood specimen	66.9	67.3	73.3	65.9

Table 3—Cooperative Measles Vaccine Field Trial (Median Number of Days of Prodrome, Fever, Rash, Confined to Bed, and School Absence, According to Diagnosis)

Diagnosis	Median Number of Days				
	Prodrome	Fever	Rash	Confined to Bed	School Absence
Regular measles	2.6	4.7	5.3	4.8	7.9
Mild measles	1.4	2.1	4.2	2.1	5.2

Samples were drawn immediately prior to the first injection and approximately one month after the third injection. A third blood sample was drawn from these same children eight months after the third injection, and a fourth blood sample is scheduled to be drawn approximately 16 months after the third injection. The first two blood specimens have been tested for measles antibody by the hemagglutination inhibition (HAI) test using the microtiter technic.

A total of 4,860 children completed the three injection treatment series. This was 93.3 per cent of the group that received the first injection. A total of 4,798 were still under surveillance on May 31, 1962. Data are presented only for this latter number.

As seen in Table 2, the age, school grade, race, and sex of the children in each of the treatment groups were comparable. Prior to vaccination, the percentage of children in each group with no detectable measles hemagglutination inhibition antibodies was essentially the same. Those children receiving the killed-live vaccine series had a slightly higher percentage of serologic susceptibles. This variation is not statistically significant.

Routine surveillance for measles incidence began in all areas on January 2, 1962, at the time the children were receiving their second injection. Two doctors in each study area were designated to appraise case histories and to determine the final diagnosis. Each appraisal included a personal conversation between the study physician and either a parent or the family doctor. This final diagnosis was made without knowl-

Table 4—Cooperative Measles Vaccine Field Trial (Incidence of Illness with Onset between 2 and 18 Weeks after the Third Injection, by Diagnosis and Treatment Group)

Diagnosis	Treatment Group				Total
	KKK	PPP	KKL	PPP	
Regular measles	5	84	0	91	180
Mild measles	15	21	3	22	61
Total	20	105	3	113	241*
Diagnosis unknown with rash	11	10	6	7	34

* Does not include ten cases which were reported late.

Table 5—Cooperative Measles Vaccine Field Trial Vaccine Effectiveness*

Vaccine Group	Illness Incidence: All Measles Cases Per cent	Illness Incidence: Regular Measles Only Per cent
KKK	82	94
KKL	97	100

* Calculated according to the formula:

$$\frac{\text{Expected Cases} - \text{Observed Cases} \times 100}{\text{Expected Cases}} = \text{Per cent Effectiveness}$$

edge of which vaccine treatment the child had received.

Although during the study, gamma globulin was given by private physicians to some children exposed to measles, the random assignment of treatments, and the double-blind nature of the study, prevented bias in this regard.

Results

Epidemic measles occurred in two of the five participating cities. These two cities accounted for 91 per cent of all illnesses reported. Through May 31, 1962, the participating investigators had submitted reports on 415 illnesses. Of these, 306 were considered to be "regular" measles, 54 cases were considered to be "mild," and 55 cases were designated as "diagnosis unknown, with rash."

In order that cases from all areas could be uniformly evaluated, criteria were established for the diagnosis of "regular" measles. These criteria were derived from an analysis of characteristics of those cases designated as measles by the individual investigators.

Considered as "regular" measles by these criteria were those illnesses diagnosed as measles and characterized by a temperature of at least 103° (oral), or a history of fever of at least four days' duration; a rash on the face, neck, and trunk of three or more days' duration; cough or coryza; and confinement to bed of at least two days' duration. Cases of measles which did not meet all of these criteria were classified as "mild." As shown in Table 3, those children experiencing "regular" measles experienced a longer prodrome, fever, and time spent in bed. These children also had more days of rash and more days absent from school.

Between 2 and 18 weeks after the third injection 241 cases of measles occurred (Table 4). Five cases of "regular" measles occurred after three injections of killed vaccine. No cases of "regular" measles occurred following the killed-live series of measles vaccines. There were 15 cases of "mild" measles after three injections of killed vaccine. Three illnesses designated as "mild" measles occurred after receiving the killed-live combination. In contrast to the vaccine groups, each of the placebo groups had over 100 cases of measles, 75 per cent to 80 per cent of which were classified as "regular" measles.

In instances where the investigator in the field was uncertain regarding the diagnosis of measles, the appraisal category, "diagnosis unknown, with rash," was used. Illnesses with this diagnosis were distributed equally among the four treatment groups. Seventeen cases occurred in the vaccine groups and 17 cases in the placebo groups.

All cases of measles, "regular" and "mild," occurring at any time after the third injection are presented graphically in Figure 1. The cumulative measles attack rates in the placebo groups climb steadily, the two placebo groups having essentially identical curves. The cumulative measles attack rates for the two vaccine groups remain low.

Calculated vaccine effectiveness is shown in Table 5. Considering all illnesses diagnosed as measles, both "regular" and "mild," occurring between 2

and 18 weeks after the third injection, a series of three injections of killed vaccine is calculated to be 82 per cent effective. After the third injection of the killed-live series of measles vaccine, 97 per cent protection is achieved.

If only "regular" measles incidence is considered, it is found that three injections of killed measles vaccine afford 94 per cent protection. Since no cases of regular measles occurred after the killed-live measles vaccine combination, the protective effectiveness of this treatment schedule is calculated to be 100 per cent.

Measles antibody titers were determined on blood samples taken one month after the third injection in those children who were initially seronegative. Figure 2 shows the per cent distribution of antibody titers for the two vaccine schedules. The median antibody titer resulting from three injections of killed measles vaccine is 10, whereas the antibody response resulting from a combination of killed and live measles vaccine reaches a median of 40. The geometric mean titer of those serums showing seroconversion is 17 for the killed vaccine schedule and 45 for the killed-live vaccine schedule. For reference, serums taken within a month after natural measles infections have, in our laboratory, shown HAI antibody titers in the range of 80.[17]

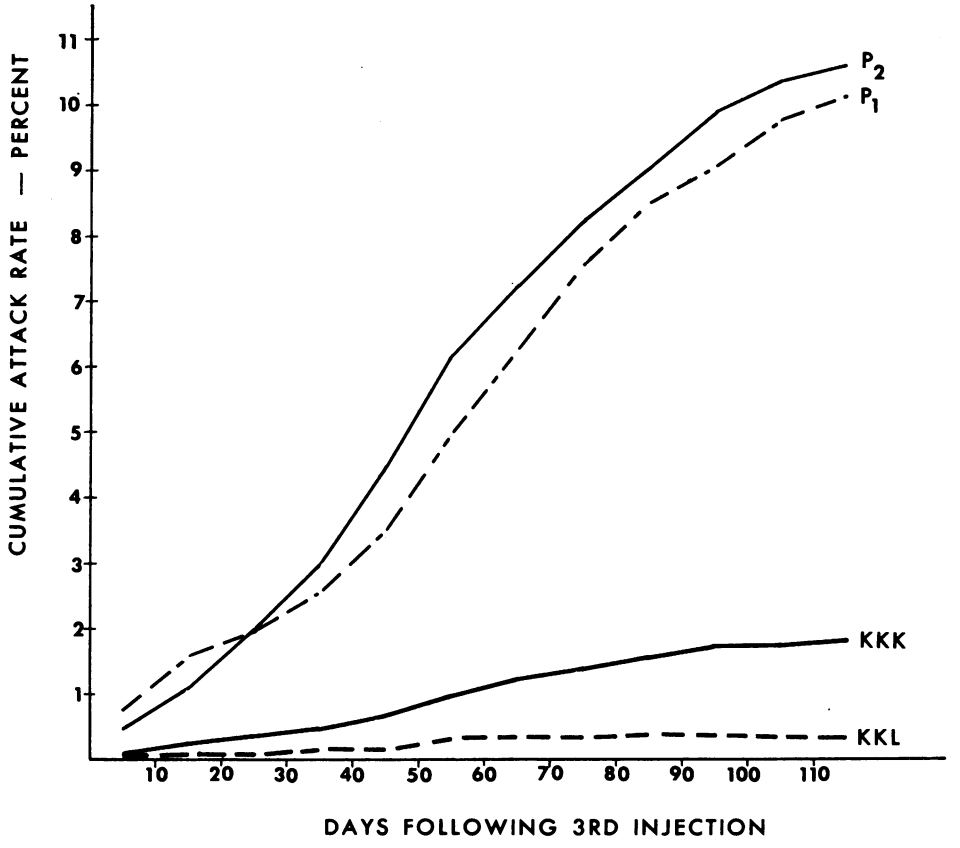
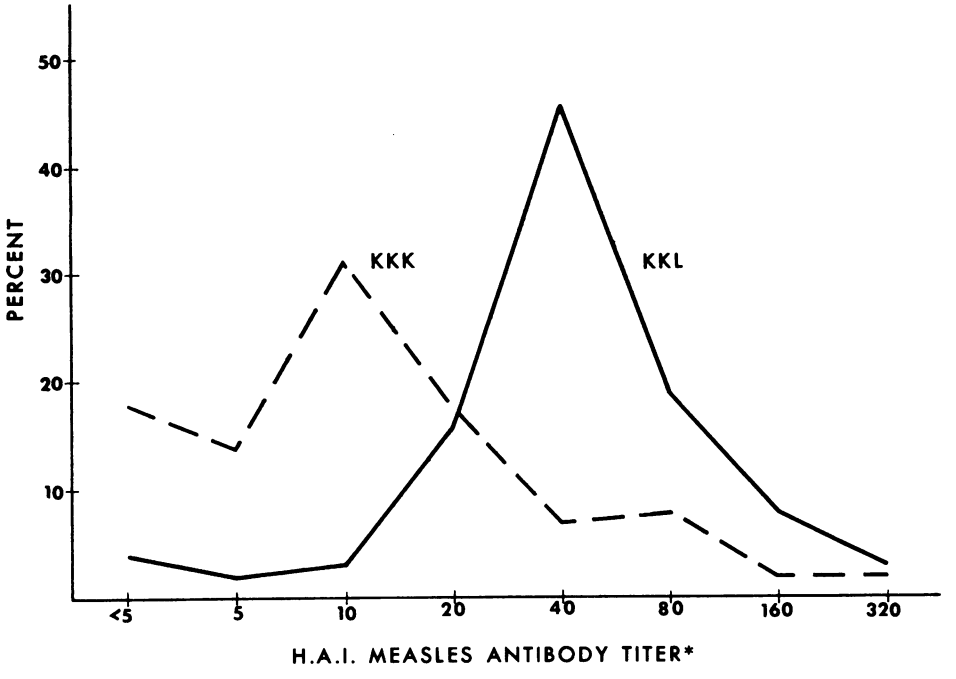


Figure 1—Cumulative Measles Attack Rate from Day of Third Injection for Each Treatment Group (By 10-Day Periods)

Figure 2—Per cent Distribution of HAI Seroconversions



* Titers expressed as reciprocal of dilution.

Summary

As reported in this study, 4,798 school children, in kindergarten, first, and second grades, divided randomly into four treatment groups, have been given three injections of 0.5 ml of killed vaccine, or two injections of 0.5 ml of killed vaccine followed by an injection of live measles vaccine, or one of two series of placebo injections. Conducted throughout as a double-blind study, close surveillance for all possible cases of measles is being maintained, and periodic blood samples for serology are being drawn on a random 10 per cent of the participating children.

Both measles vaccine schedules provided significant protection during the four-month surveillance period following the third injection. Contrasted to over 100 cases of measles occurring in each of the two placebo groups, those receiving three injections of killed vaccine had 20 cases of measles for a calculated effectiveness of 82 per cent; those children receiving two injections of killed vaccine followed by one of live measles vaccine experienced but three cases of measles for an effectiveness of 97 per cent.

The distribution curves of the antibody levels evoked by the two vaccine schedules revealed significantly higher hemagglutination inhibition titers among those receiving the killed-live measles vaccine schedule as compared to those receiving three injections of killed vaccine.

This study population will continue to be kept under illness and serologic surveillance to obtain further information on the duration of protection afforded by the two vaccine schedules.

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