Evaluation of a trivalent measles, mumps, rubella vaccine in children

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LIVE ATTENUATED VIRUS VACCINES can be administered simultaneously without increase in reactivity or diminution in immunologic responses.[1] Recently, a second measles, mumps, and rubella trivalent vaccine has been licensed. This study describes the reactivity and immunologic efficacy of this newer trivalent vaccine.

MATERIALS AND METHODS

Vaccine. The vaccine was a combination of Schwarz strain live, attenuated measles virus,[2] Jeryl Lynn strain live, attenuated mumps virus,[3] and Cendehill strain live, and attenuated rubella virus.[4] Three different production lots were used in this study. All lots contained at least 1,000 50% tissue culture infective doses of measles and rubella viruses and 5,000 $TCID_{50}$ of mumps virus. The trivalent vaccine was dispensed into single dose vials, lyophilized, and stored at 5°C until administered.

Placebo. The placebo used in the study was identical to the vaccine in all respects except it did not contain virus.

Serology. All serologic assays were performed in the Assay Laboratory of The Dow Chemical Company in Zionsville, Indiana. Antibodies to measles and rubella viruses were determined by the hemagglutination inhibition method in microtiter plates.[5, 6] Four units of hemagglutination antigen were used; the end point was taken as the highest serum dilution that completely inhibited agglutination of the test erythrocytes. Mumps antibody titers were determined by the *VERO* cell microtiter serum neutralization technique.[7] If postinoculation antibody was not detected by this technique, paired sera were retested undiluted and at 1:2 dilution by a plaque technique in *VERO* cells (Kenny, M. T. and Schell, K. R., to be published).

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Table I. Percentage of children exhibiting positive clinical findings from Day 7 through Day 21 after inoculation

	Vaccinees (%)*	*Placebo subjects (%)*
Temperature elevation†: Degrees above normal‡		
1.5-2.4°F	10.6	5.7
2.5 - 3.4°F	0.6	5.7
3.5 - 4.4°F	3.1	0.0
4.5 - 4.9°F	1.2	0.0
Qualitative findings§:		
Rash	12.0	5.0
Lymphadenopathy	1.1	2.5
Coryza	2.2	10.0
Rhinitis	1.1	10.0
Cough	2.7	2.5
Other	19.1	20.0

*All vaccinees are triple susceptible. Twenty-three vaccinees and five placebo subjects were omitted from the upper part of the table because of inadequate temperature records.
†One-hundred sixty vaccinees and 35 placebo subjects
‡Normal is defined as 99.6°F rectal (163 children), 98.6°F oral (6 children), and 97.6°F axillary (26 children).
§One-hundred eighty three vaccinees and 40 placebo subjects.

Abbreviations used
$TCID_{50}$: 50% tissue culture infective doses
HI: hemagglutination inhibition
SN: serum neutralization
GMT: geometric mean titers

Children were considered susceptible to each disease if antibody was not detectable (measles HI titer $< 1:2$; mumps SN titer $< 1:2$; rubella HI titer $< 1:8$) in the preinoculation serum. Seroconversion after inoculation was determined by the appearance of antibody in the postinoculation serum sample of a previously susceptible child. Pre- and postvaccination paired sera were always tested simultaneously. All assays were done with double-blind samples and the results were decoded, tabulated, and analyzed by computer.

Population. Subjects were admitted to the study from a private pediatrician's office. Criteria for admission included: (1) 11 months to four years of age; (2) absence of any history of natural measles, mumps, or rubella, or immunization against these diseases; (3) parental consent; and (4) the absence of any of the usual medical contrain-

Table II. Immune responses of triple susceptible children 1 to 4 years of age inoculated with trivalent (measles/mumps/rubella) live-virus vaccine or placebo

	Number of subjects	*Immune responses*								
		Measles seroconversion			*Mumps seroconversion*			*Rubella seroconversion*		
		No.	*%*	*GMT*	*No.*	*%*	*GMT*	*No.*	*%*	*GMT*
Lot 1	62	62	100.0	43.7	59	95.2	4.1	61	98.4	21.7
Lot 2	65	64	98.5	36.0	65	100.0	3.9	64	98.5	23.6
Lot 3	55	55	100.0	37.2	55	100.0	4.7	52	94.5	21.2
Totals	182	181	99.4	38.9	179	98.4	4.2	177	97.3	22.2
Placebo	40	0	0	0	0	0	0	0	0	0

dications to immunization with measles, mumps, or rubella live, attenuated virus vaccines.

Study design. A randomized, double-blind design was used to distribute the study population among the three lots of vaccine and the placebo in a ratio of one placebo to every five vaccinees. Pre-inoculation blood samples were collected, and vaccine or placebo administered. Double-blind observations for possible vaccine reactions and intercurrent illnesses were made approximately three times per child during the period from Day 7 to Day 21. Additional observations were recorded after Day 21 in the event of illness, and an interval history was recorded for each child at the time an eight-week blood sample was drawn. The results of these observations were decoded and tabulated by computer.

RESULTS

Two hundred and eighty-two children participated in the study. Two hundred and twenty-five of the children were one year old, and 34 children were between 11 and 12 months of age. Overall 91.9% of the children were triple susceptible. There was a total of 709 follow-up clinical evaluations excluding the evaluations made at the time of collection of the eight-week blood sample. No local reactions were reported.

The frequencies of clinical findings between Days 7 and 21 are presented in Table I. Temperature elevations tend to occur more often in vaccinees, but the excess frequency in vaccinees (4.1% overall and 4.3% at $\geq$ 3.5°F) is not statistically significant (Fisher's exact probability: p = 0.37 overall and 0.24 at $\geq$ 3.5°F).

Other clinical findings were of low frequency in both susceptible and placebo subjects. The higher frequency of rash reported in vaccinated triple susceptible subjects compared with susceptible placebo subjects was not statistically significant ($\chi^2 = 0.752$, $0.1 < p < 0.5$). No limb or joint symptoms were reported either before or after Day 21.

Paired sera were obtained from 222 triple susceptible subjects one to four years of age. The serologic results from these children are summarized in Table II. The seroconversion rates in triple susceptible vaccinees one to four years of age ranged from 98.5% to 100% for measles, from 96.8% to 100% for mumps, and from 94.5% to 98.5% for rubella. The geometric mean titers of antibodies against all three viruses were as high as those found after monovalent vaccination.

Paired sera were obtained from 33 triple susceptible infants who were 11 months old at the time of vaccination. Of these, 29 were vaccinees and four were placebo subjects. Among these infant vaccinees seroconversion rates were 93.1% for measles and rubella and 96.5% for mumps, and the GMT's were 36.2 for measles, 4.3 for mumps, and 23.2 for rubella.

None of the recipients of the placebo experienced seroconversion.

DISCUSSION

The availability of effective trivalent vaccines has important implications in achieving successful immunization programs. Besides being more economical, the trivalent vaccines permit fuller vaccine coverage in the segments of the populations which have been traditionally hard to immunize. Reduction in the number of visits required for immunization makes this possible.

Measles, mumps, and rubella live-virus vaccines are generally considered to be less than fully effective in children less than one year old because of the occasional persistence of maternal antibodies. In this study, 29 11-month-old triple-susceptible triple vaccinees gave seroconversion rates and GMT's within the ranges to be expected from older children receiving the same vaccines alone or combined. However, this number of infant vaccinees is too small to justify advocating administration of this trivalent vaccine prior to one year of age. Therefore, this vaccine should not be given to children under

one year of age unless required by epidemic conditions. Infants thus vaccinated should be revaccinated after they have attained one year of age unless an antibody response to the earlier vaccination can be documented.

A trivalent measles, mumps, rubella vaccine, M-M-R, has been available for more than two years. The trivalent vaccine we evaluated has been recently licensed and provides physicians with a choice of product. The two vaccines differ in the strains of measles and rubella, but utilize similar dosage of all three components. The trivalent vaccines have resulted in adequate antibody response, little reactivity, and indications for persistence of antibody similar to the monovalent vaccines.[8]

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Defective neutrophil chemotaxis in patients with Down syndrome

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DOWN SYNDROME (trisomy 21) is associated with increased susceptibility to infection. This phenomenon may be due partially to such defects in leukocyte function as decreased phagocytosis[1] and bactericidal capacity[2] and poor nitroblue tetrazolium dye reduction.[2] We have recently studied chemotactic migration of polymorphonuclear leukocytes obtained from children with Down syndrome and have observed significantly decreased values when compared to cells from normal control subjects.

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SUBJECTS AND METHODS

Ten infants and children (six boys and four girls) with Down syndrome, currently free of infection, were studied. Their ages ranged from 9 months to 12 years with a median of 4.5 years; they had never been in an institutional environment. The diagnosis of Down syndrome was confirmed as trisomy 21 by cytogenetic studies in all cases. An equal number of age-matched children (admitted to the hospital for elective surgery) served as control subjects.

Abbreviations used
HBS: Hanks balanced salt
NBT: nitroblue tetrazolium

Chemotaxis was performed by the technique of Boyden[3] as modified by Baum and associates.[4] Leukocytes were harvested by methyl cellulose sedimentation as described previously.[4] Cell counts were adjusted by adding Hank balanced salt solution. Three-tenths of a milliliter of this suspension was used to deposit 1.0×10^6 to 2.6×10^6 cells (with 75-90% granulocytes) to a 3μ millipore filter, utilizing a Shandon Elliot cytocentrifuge. The filters were then placed in a Sykes Moore tissue culture chamber. The upper compartment was filled with HBS while the lower compartment contained a 20% mixture of type AB serum in HBS containing *Escherichia coli* endotoxin (Difco Laboratories), 1 μg/ml of HBS.