A Field Trial with a Live Measles-Mumps-Rubella Vaccine

Successful Use of a New Combination of Virus Strains

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Three lots of Lirutrin (measles-mumps-rubella live, attenuated virus vaccine) were evaluated in a double-blind, placebo-controlled clinical study involving 273 children. The vaccine consisted of a combination of Schwarz strain measles, Jeryl Lynn strain mumps, and Cendehill strain rubella vaccine viruses. The frequency of positive clinical findings was essentially the same in susceptible vaccinees, immune vaccinees, and placebo recipients; indicating that the observed symptoms were not caused by the vaccine. Antibody assay of paired serum samples revealed that measles, mumps, and rubella seroconversion rates in triple susceptible vaccinees were excellent, ranging from 96 to 98 per cent with all three lots combined. Results of this study show that Lirutrin trivalent vaccine is well tolerated and highly effective.

COMBINED VACCINES in pediatric use lead to fewer patient visits and reduce the overall cost of immunization, without loss of immunizing effectiveness. A recent study revealed that Schwarz strain measles and Cendehill strain rubella vaccines were safe and effective when administered as a bivalent, single injection.[8] The present study was conducted to determine the clinical reaction rate and immunizing efficacy of a trivalent mixture of Schwarz strain measles, Jeryl Lynn strain mumps, and Cendehill strain rubella vaccines (Lirutrin) administered as a single injection.

Selected as the locale of these studies were certain communities in Panama in which the children are highly susceptible to the three infectious diseases represented by the vaccine. The populations here consist of the Cuna Indians of the San Blas Islands, the native Panamanians (a mixed Indian race of the interior of Panama), and children living in the city of Colon who have a racial background including African, Indian, Spanish, and Oriental.

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TABLE 1. *Age Distribution of the 273 Children Used in this Study, and of Those Triply Susceptible*

Age	Vaccinees			Placebo Recipients	Per Cent Triply Susceptible*
	Lot 1	Lot 2	Lot 3		
<1	4	2	2	2	70.0
1	14	17	14	11	53.6
2	16	11	13	8	29.2
3	11	13	14	10	21.0
4	17	12	15	6	16.0
5	6	7	7	5	12.0
6	6	4	7	6	8.7
7	2	5	3	0	20.0
8	0	1	0	1	0.0
9	0	0	1	0	0.0
Totals	76	72	76	49	27.8

* Susceptible to measles, mumps, and rubella.

Immunization records of the Ministerio de Salude, Republic of Panama indicated that none of the components of the vaccine had ever been given in these communities and, further, there were no records of any epidemics of measles, mumps, or rubella in the past five years in these areas.

Another factor in the choice of these areas was the high incidence of complications of measles among the Cuna and interior Indians. This was evidenced by local hospital records and by accounts by the Cunas of large epidemics in previous years which caused deaths of large numbers of children.

Materials and Methods

Vaccine

Lirutrin is a combination of Schwarz strain (Lirugen) measles vaccine[9,10] licensed in 1965, Jeryl Lynn strain mumps vaccine[2,3,11] originally licensed in 1967, and Cendehill strain rubella vaccine[1,6] originally licensed in 1969. Three lots of Lirutrin were used in this study. Each dose contained a minimum of 1,000 50 per cent tissue culture infective doses ($TCID_{50}$) of measles and of rubella vaccine viruses and 5,000 $TCID_{50}$ of mumps vaccine virus. The vaccines were produced at the Biological Laboratories of The Dow Chemical Company, Indianapolis, Indiana over a period of about six months. For each child, a single dose vial of Lirutrin (or placebo) was reconstituted with sterile diluent from a prefilled syringe just prior to subcutaneous inoculation.

Placebo

Placebo was prepared from the same materials as the vaccine, but without added virus. Whether lyophilized or reconstituted, the placebo was indistinguishable from the vaccine in appearance.

Serology Methods

Antibodies to measles and rubella viruses were determined double-blind by the hemagglutination-inhibition (HI) method in microtiter plates. Sera for testing were pretreated with kaolin (measles HI test) or with manganese chloride and heparin (rubella HI test) and adsorbed with the appropriate test erythrocytes. Erythrocytes of newly hatched chicks were used as the indicator in the rubella HI test, and African green monkey erthrocytes were used in the measles HI test. Serial twofold serum dilutions were tested against four units of HA antigen. The highest serum dilution that completely inhibited agglutination of the test erythrocytes was the endpoint. Although these microtiter methods yield significantly lower titers than conventional macrotiter methods, this disadvantage is counterbalanced by the convenience of the microtiter system for large numbers of assays. Pairs of sera which failed to show obvious seroconversion in the microtiter test were retested by the conventional macrotiter method.

Mumps antibody titers were determined by the Vero cell microtiter serum neutralization (SN) technique.[4] When postinoculation anti-

TABLE 2. *Distribution of Axillary Temperature Readings from the Seventh Through 21st Day Postvaccination*

Axillary Temperature Intervals in Degrees Fahrenheit	Triply Susceptible Vaccinees (All Lots) (N** = 52†)	Susceptible* Placebo Recipients (N = 36)	Triply Immune Vaccinees (All Lots) (N = 20)	Triply Immune Placebo Recipients (N = 4)
<98.1	14 (26.9)‡	5 (13.9)	5 (25.0)	1 (25.0)
98.1– 99.0	29 (55.8)	26 (72.2)	14 (70.0)	1 (25.0)
99.1–100.0	7 (13.5)	3 (8.3)	1 (5.0)	2 (50.0)
100.1–101.0	2 (3.8)	2 (5.6)	0	0
>101.0	0	0	0	0

* Placebo susceptibility is defined as a patient's being susceptible to any one vaccine component; however, 12 of the 36 children were triply susceptible.
** N = Number of subjects observed.
† Includes five children without an eight-week serum sample.
‡ Number and per cent of children within the indicated temperature interval.

body was not detected by this technique, paired sera were retested undiluted and at 1:2 dilution by a plaque reduction technique in Vero cells.[5]

Children were deemed susceptible to each disease when their preinoculation serum did not contain detectable antibody (measles HI titer <1:8; mumps SN titer <1:2; rubella HI titer <1:8). Seroconversion after inoculation was defined as the appearance of antibody in the postinoculation serum sample of a child whose serum was previously negative.

Children Tested

Approximately half the children enrolled in the study were from the Red Cross Nursery School in the City of Colon. In Colon, measles is more or less continually endemic, with seasonal variation.

The rest of the children were enrolled from rural areas in the Provinces of Colon and San Blas. In these relatively isolated areas, measles occurs only as an epidemic, the last of which had been several years before.

The total number of children enrolled, prebled and injected, was 273. The essentials for entry into the study series were: 1) informed parental consent; 2) absence of any history of natural measles, mumps, or rubella, or immunizations against these diseases; and 3) absence of any of the usual medical contraindications of immunization with live virus vaccines. Entry into the study was offered primarily to children aged one through four years, but occasionally parental insistence necessitated admission of a few younger (age 10 to 11 months) or older children.

Study Design

Three lots of vaccine and one lot of placebo were used. A randomized double-blind design was used to distribute these within the study population, in a ratio of one placebo subject to approximately five vaccinees. After the injections (Day 1), each child was examined clinically for possible vaccine reactions and intercurrent illnesses approximately three times between Day 7 and Day 21. The axillary temperature was measured during each examination. The examiners were ignorant of what each child had received. The results of these double-blind clinical observations were decoded and tabulated by a computer. Eight weeks after the injection, a second blood sample was drawn and additional clinical data were obtained.

The essentials for entry into the study series were: 1) informed parental consent; 2) absence of any history of natural measles, mumps, or rubella, or immunizations against these diseases; and 3) absence of any of the usual medical contraindications to immunization with live virus vaccines.

The distributions with respect to age of the 273 children who received the three different

vaccines or placebo are shown in Table 1. The randomized double-blind code effectively provided the desired distributions of children with respect to the three lots of vaccine and the one lot of placebo. The male/female ratio was 0.9. A total of 75 children susceptible to all three diseases (*i.e.*, triple susceptible) entered the study.

Clinical Symptoms Following Lirutrin Vaccine

Inquiries at the time of the first follow-up visit failed to elicit any history of any injection site reactions or of any immediate symptoms following the injection.

From the seventh through the 21st day after vaccination, 674 clinical visits were completed. There were also 223 clinical follow-up visits at the time the 8-week blood sample was taken, and notations were made of any history of symptoms since the 21-day follow-up visit.

The distribution of temperature readings is shown in Table 2. In addition to the placebo control group built into the study design, 20 vaccinees who were found to have been immune to all three viruses (*i.e.*, triple immune) provide another standard against which the triple susceptible vaccinees may be compared. Statistical analysis showed no significant temperature difference between the latter and either of the control groups. Even at the highest temperature range (100.1 to 101.0 F), the difference between triple susceptible vaccinees (3.8%) and triple immune vaccinees (0.0%) was not significant (chi-square = 0.79, $p > 0.1$).

The frequency of clinical findings other than fever seven thru 21 days postvaccination are shown in Table 3. None of the differences between triple susceptible vaccinees and either immune vaccinees or susceptible placebo recipients was statistically significant in the chi-square test. Therefore, on a statistical basis, the observed symptoms were not attributable to the vaccine.

Immunity Following Lirutrin Vaccine

Eighth week postinoculation blood samples were obtained from 209 children, of whom 59 (47 vaccinees and 12 placebo subjects) had been triple susceptible at the time of inoculation. Table 4 shows the seroconversion rates and geometric mean titers (GMT)

TABLE 3. *Positive Findings in Double-Blind Clinical Examinations from the Seventh through the 21st Day after Vaccination*

	Triply Susceptible Vaccinees (All Lots)	Susceptile* Placebo Recipients	Triply Immune Vaccinees (All Lots)
	(N** = 52)	(N = 36)	(N = 20)
Local reactions	0	0	0
Rash	3 (5.8)†	1 (2.8)	0
Lymphadenopathy	1 (1.9)	1 (2.8)	0
Conjunctivitis	1 (1.9)	0	0
Otitis media	0	0	0
Coryza	0	0	0
Rhinitis	2 (3.8)	0	0
Pharyngitis	0	0	0
Bronchitis	0	0	0
Cough	0	0	0
Headache	0	0	0
Parotitis	0	0	0
Orchitis	0	0	0
Limb or joint	0	0	0
Paresthesia	0	0	0
Other‡	8 (15.4)	2 (5.6)	0

* Placebo susceptibility is defined as a patient's being susceptible to any one vaccine component.
** Number of subjects observed.
† Number and per cent of children with the indicated symptom.
‡ Other symptoms include malaria, malnutrition, anemia, diarrhea, G. I. symptoms, etc.

TABLE 4. *Seroconversion Rates and Geometric Mean Antibody Titers, According to Vaccine Lot, Among Initially Triply Susceptible Children Given Lirutrin and Bled Eight Weeks Later*

	Number of Subjects	Seroconversions and Geometric Mean Titers					
		Measles		Mumps		Rubella	
		(%)	GMT	(%)	GMT	(%)	GMT
Lot 1	16	100	51.5	94	6.3	94	30.6
Lot 2	19	95	48.9	100	4.8	95	26.4
Lot 3	12	100	71.8	100	4.0	100	24.0
Totals	47	98	55.0	98	5.0	96	27.0
Placebo	12	0	0	0	0	0	0

of the triple susceptible subjects. Seroconversion rates ranged from 95 to 100 per cent for measles and from 94 to 100 per cent for both mumps and rubella. The GMTs were 55.0 for measles, 5.0 for mumps, and 27.0 for rubella. The immune responses induced by this trivalent vaccine did not differ significantly from those reported for the three monovalent vaccines given separately.[1-3,6,9-11]

Of the ten subjects under one year of age, blood samples were obtained eight weeks postvaccination from eight, of whom six (five vaccinees and one placebo subject) had been triple susceptible. All five triple susceptible vaccinees seroconverted to all three vaccine components except for one infant who failed to convert to rubella. The GMTs developed by these infants were 73.5 for measles, 5.3 for mumps, and 22.5 for rubella.

Thirty-three vaccinees in the study were susceptible to only one vaccine component and all 33 seroconverted to that particular component (one to measles, titer 128; eight to mumps, GMT 4.9; and 24 to rubella, GMT 31.1). Essentially, no difference existed between the titers developed by these monosusceptible vaccinees and those developed by the triple susceptible vaccinees. Double susceptible vaccinees also responded similarly.

No seroconversion occurred in any of the placebo subjects.

Discussion

Clinical safety and efficacy of each of the components of Lirutrin have been repeatedly documented.[1-3,6,8-11] Giving these licensed monovalent products to millions of children[7] without untoward effects is compelling evidence of their safety and efficacy.

The main purposes of the present study were to detect whether any special symptoms might result from these vaccines in combination and to observe whether any increase might occur in either frequency or severity of mild side effects known to be associated with the individual components. Symptoms such as fever, rash, arthritis, arthralgia, and parotitis were of particular interest. The observations made in this study show the vaccine components to be comparible *in vivo* with respect both to efficacy and to freedom from undesirable reactions.

These observations indicate that there is neither viral nor immunologic interference between any of the components of the trivalent vaccine.

Some of the observed fevers and rashes may have been vaccine-induced, but the frequency of these known minor reactions to measles and rubella vaccines did not seem enhanced when these vaccines were given in a trivalent mixture with mumps vaccine. Similarly, the nonoccurrence of other symptoms in this study population indicates that these are not stimulated by combination of the vaccines.

In this study, all the Lirutrin components induced seroconversion in 96 to 98 per cent of the triply susceptible children. The levels of immunity, expressed as GMTs, induced in

these children by this trivalent vaccine were comparable to those induced by the individual components used as monovalent vaccines. Furthermore, the trivalent vaccine induced equivalent GMTs in triple susceptible and single susceptible vaccinees. These observations indicate that there is neither viral nor immunologic interference between any of the components of the trivalent vaccine.

Data from this study indicate that Lirutrin (trivalent, live, attenuated measles-mumps-rubella vaccine) is well tolerated and highly effective.

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Venereal Disease Education: The Concept of Love

In our society, love has frequently become a euphemism for sex. Therefore many youth search for a lasting relationship through sex relations. In this search, indiscriminate sexual contacts increase. A better understanding of what is desired in a love relationship, what commitments and responsibilities are involved and whether the emotional void and loneliness that some students may feel can be filled solely through sex relations should be examined in class from various perspectives. Students must learn to understand the role of sex in a love relationship.

This concept demonstrates how an additional dimension can be added to venereal disease education in the health education classroom or when counseling an individual student. It presents a difficult task for the health educator but much can be accomplished. Dealing with students' motives and preparing lessons centering around challenging attitudinal and behavioral concepts and issues requires innovativeness, insight, and concern. By complementing the knowledge and the facts that often comprise the entire venereal disease education program, the gap between knowledge and behavior can be narrowed further.—*Stanley Snegroff, Ed.D. in* The Journal of School Health; *January, 1975.*