MERIEUX INSTITUTE, INC.

April 28, 1983

John C. Petricciani, M.D.
Director
Office of Biologics HFN-800
National Center for Drugs & Biologics
8800 Rockville Pike
Bethesda, Maryland 20205

REFERENCE: 83-087

Dear Dr. Petricciani:

Enclosed is a report from Dr. A. Marshall McBean and co-investigators on a comparison of oral and Merieux killed polio vaccine.

The Merieux vaccine was produced from primary monkey kidney cells, however, it was made by the same basic methods used to produce the current polio vaccine from VERO cells.

This data was recently presented at the International Polio Symposium held at PAHO, Washington, D.C., March 14-17, 1983.

Because of the similarity of the final products, which differ only in cell substrate, this data on potency and efficacy is submitted in support of this application under Item 26.d.

Sincerely,

Pinya Cohen

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A Comparison of the Serologic Response to Oral and Injectable Trivalent Polio Vaccine

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Running Head: Serologic Response to IPV and OPV

1. The authors gratefully acknowledge the assistance of the nursing and medical staff of the pediatric clinics of the cooperating agencies. In particular we thank Dr. Helen McAllister of the Prince George's County Health Department; Dr. Lindsey Grossman and Dr. John Neff of the Baltimore City Hospitals; Dr. John Krager of the Baltimore County Health Department, Dr. Venita Thweat of the Baltimore City Health Department; and Dr. Ruth Steerman of the Prince George's County General Hospital.

2. This research is supported by contract #200-80-0512(P) of the Centers for Disease Control, United States Department of Health and Human Services.

3. Informed consent was obtained from the parents of children in the study and guidelines for human experimentation of the United States Department of Health and Human Services and the Johns Hopkins University School of Hygiene and Public Health were followed in the conduct of the clinical research.

4. Please address requests for reprints to Dr. A. Marshall McBean, Johns Hopkins University School of Hygiene and Public Health, 615 North Wolfe Street, Baltimore, Maryland 21205

ABSTRACT

American children two months of age were randomly assigned to two groups which received either the commercially available oral trivelant polio vaccine (OPV) or an injectable trivalent polio vaccine (IPV) with a confirmed minimum D-antigen content of 27, 3.5 and 29 units for polio virus type I, II and III respectively. Vaccine was given at 2, 4, and 18 months of age. Sera was obtained at 2, 4, 6 months of age on 439 children and on 85 children at 18 and 20 months of age and examined for neutralizing antibodies.

The percent of children with detectable antibodies and the reciprocal geometric mean titers (GMTs) were similar for both groups at two months of age for all three polio types. At twenty months of age, all children but one had detectable antibodies to all three polio types. Significantly higher GMTs against types I and III were noted at twenty months for the IPV group.

I. Introduction

Protection of the United States population against poliomyelitis has been greatly facilitated by the availability of two very effective and safe types of vaccine: inactivated poliovirus vaccine (IPV) and live attenuated oral poliovirus vaccine (OPV). During the period from 1955 to 1961, immunization efforts using IPV were successful in reducing the number of reported paralytic polio cases from 13,850 (7.9/100,000 population) in 1955 to 820 (0.7/100,000) in 1961 [1]. In spite of this tremendous achievement, "The Cutter Incident" [2] in which the virus in the IPV was not inactivated, and the contamination of monkey kidney cells in which the IPV virus was grown by SV-40 virus which is oncogenic in hamsters, helped create an environment in which the use of IPV was rapidly discontinued after OPV became available in 1962. The decision to use OPV was also based on its ease of administration and acceptance; expected long lasting (perhaps life-long) immunity; rapid production of bowel immunity which could interrupt wild virus transmission, even in epidemic situations; and the spread of OPV virus to unvaccinated persons which could induce immunity in these people [3,4]. The continued reduction in the number of cases of paralytic disease in the era of OPV use has been reported annually by the Center for Disease Control (CDC), Atlanta, Georgia, U.S.A. By 1972, the number of cases has been reduced to 29 per year (0.01/100,000). During the years 1973-79, 82 cases of paralytic polio have been reported to CDC, an average of 12 cases per year.

Thus, the efficacy of both the IPV and OPV in inducing immunity and protecting recipients is well documented. However, there are reports of areas where children were given IPV and antibody levels were detectable in only 65 to 74% of the children who had received multiple doses of IPV [5]. For IPV, the seroconversion rates, post-immunization titers and the duration of immunity have been proportional to the potency of the vaccine; i.e., are dose-dependent

[6]. Vaccine production methods reported by (b) (6) of the Rijks Instituut Voor de Volksgezondheid, Bilthoven, The Netherlands, allow for higher concentrations of vaccine antigens than were attainable in previous IPV.

This study will compare the immunologic response in American infants given three doses of IPV made by the new production techniques with three doses of commercially available OPV. Data available through February, 1983 will be presented.

II. Materials and Methods

Participants: Children attending Well-child Clinics in Maryland were enrolled in the study and randomly assigned to receive either the OPV or the IPV. Children entered the study when they were between 6 and 13 weeks ("2 months") of age, and either OPV or IPV was administered at that time. Sixty days later, when the child was "4 months" of age, a second dose of the same vaccine was given. A third dose of the same polio vaccine was given at "18 months" of age. Diphtheria, Tetanus, Pertussis vaccine (DTP) and either an oral or injectable polio placebo were administered at the same time as the polio vaccines. As shown in Table 1, blood specimens were taken at 2, 4, 6, 18 and 20 months of age.

Vaccines: The OPV used was the commercially licensed available vaccine manufactured by Lederle Laboratories (Wayne, New Jersey, U.S.A.). It contained 800,000 $TCID_{50}$ of type I, 100,000 $TCID_{50}$ of type II, and 500,000 $TCID_{50}$ of type III per 0.5cc dose. The IPV was manufactured by the Merieux Institute (Lyon, France). It had a minimum potency of 27 D-antigen units of type I, 3.5 D-antigen units of type II, and 29 D-antigen units of type III per 0.5cc dose. The DTP contained (b) (4) Lf of diphtheria toxoid, 5 Lf of tetanus toxoid and 4 Units of pertussis per 0.5cc dose. The potency of the IPV, as measured by D-antigen content, was confirmed every three months at the Rijks Instituut.

Blood Specimen Handling: After collection, blood specimens were allowed

to clot, and the serum was drawn off. Specimens were then refrigerated and frozen within 4 to 8 hours. They were stored at -20°C until examined in the laboratory. Specimens were coded prior to being sent to the laboratory to insure unbiased laboratory analysis.

Laboratory Testing: Serum polio neutralizing antibodies were measured at the Bureau of Biologics, FDA, DHHS, Bethesda, Maryland (U.S.A.) by a virus cytopathic effect (CPE) neutralization test in microtiter trays (96 well, flat-bottomed, Microtest II, Falcon, Oxnard, CA). Each day a known serum prepared by the Rijks Instituut for each polio type was tested with the experimental sera. A conversion factor was then calculated to convert the observed reciprocal of the serum dilution which neutralized CPR in 50% of the wells to International Units (IU).

III. Results

Of the 558 children enrolled in the study to date, serum specimens from 484 have been analyzed for neutralizing antibodies. Of the 119 children not included in the analysis, 103 have been lost to follow-up, and sixteen were deleted because of lost specimens, broken collection tubes, or insufficient data. Therefore, 439 children comprise the study population, of which 196 received OPV, and 243 received IPV. All of these children have completed their 6-month visit, and 85 have completed their twenty-month visit.

As a confirmation of the randomization process, the sex distribution, the number of siblings living with the participants, and the number of siblings who received oral polio vaccine during the time of the study were similar for the two study groups. In addition, the percentage of children with detectable antibodies and the reciprocal geometric mean titers (GMTs) to the three polio virus types were the same for the children in each vaccine group at two months of age (Tables 2 and 3).

Comparing the two vaccine groups at each age for each virus type, there is

no difference in the percent of children in each group with detectable antibodies. Approximately 25% of all children do not have antibodies against type III at 2 months of age, but this decreases to 17% at 4 months of age and 5% or less, from 6 months on. At 6 months of age (2 months after the second dose of vaccine), a minimum of 93% of the children have antibodies against two polio types, I and II. The percent is unchanged between 6 and 18 months. At 20 months (2 months after the third dose of vaccine), all but one child has demonstrable antibodies.

At four months of age, the GMTs in the OPV group are significantly higher for type II and type III virus, compared with themselves at 2 months of age and with the IPV group at 4 months of age. The GMT against type I is similar for both vaccine groups and shows no change from 2 months of age. At six months of age, the GMT against type I poliovirus is significantly higher in the IPV group, and the GMT against type II is significantly higher in the OPV group. The GMTs against type III are similar in both groups.

The results from the analysis of the eighty-five children who have completed the 18 and 20-month visits reveal that, at eighteen months, the GMT in the OPV group remains significantly higher than the IPV group for type II polio virus. At twenty months, the GMTs against type II have become similar for both vaccine groups, while the GMTs against types I and III are now significantly greater for the IPV group.

IV. Discussion

An ideal study of the serologic response to polio vaccines would involve the administration of vaccine to children without antibodies to any of the polio virus types (triple negative children). Enrolling children into this study when they are 2 months of age precludes that possibility. In fact, only 12 of the 439 children were triple negative upon entry into this study, and three others were triple negative at 4 months of age. Thus, discussion of our results will

focus on the ability of the two vaccines to stimulate antibody production and protect the entire group of children given each vaccine.

If we take the presence of detectable serum neutralizing antibodies to indicate protection against polio, then both vaccines as well as residual maternal antibodies protect a similar percent of children during their first six months of life even though at 4 months of age the antibody level, as measured by the GMT, is lower in the IPV group to types I and II. The equivalency of the two vaccines in stimulating demonstrable antibodies is verified by the results at 18 and 20 months of age.

Although the percent of children with detectable antibodies at 4 months is not significantly greater than at 2 months in either group, the immunizing effect on the children receiving the first dose of OPV can be seen for types II and III by the increases in the GMTs. For the IPV and the type I oral vaccine, the GMTs decrease or remain the same after 1 dose of vaccine. The lower response to the IPV at 4 months of age is probably due to the presence of maternal antibodies in the children who received IPV at 2 months of age. On the other hand, the first dose of OPV, particularly types II and III, is able to multiply in the intestine, and stimulate the production of measurable serum antibodies at 4 months of age.

The ability of antibodies to type III to reach the same level for both OPV and IPV and a higher level for IPV to type I after the administration of the second dose of IPV may reflect either a significant primary response due to the high potency of the vaccine in the presence of declining maternal antibodies at the time of this dose, or the presence of an unmeasurable response to the first dose of IPV which is then boosted by the dose given at 4 months of age. The booster effect of the third dose of IPV is clearly seen by the great increase in GMTs to all three types between 18 and 20 months. The duration of protection cannot be estimated. However, it is likely that the higher the level of antibodies the more long lasting they will be.

Currently the Advisory Committee on Immunization Practice recommends three doses of the previously available IPV in the first year of life with a booster at 18 months. The preliminary data from this study indicates that 2 doses in the first year of life will probably be sufficient. This schedule is effective even when begun at 2 months of age when maternal antibodies are high.

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TABLE I

Schedule of immunizations and blood collection

Immunizations	2 Months	4 Months	6 Months	18 Months	20 Months
Dose of either OPV or IPV	1	2	-	3	-
Dose of DTP	1	2	3	4	-
Blood Collection	yes	yes	yes	yes	yes

Table 2

A Comparison of the Serologic Response to Oral and Injectable Trivalent Polio Vaccine

Number and Percent of Children 2, 4, 6, 18 and 20 Months of Age with Detectable Antibodies to the Three Types of Wild Polio Virus

	Polio Virus Type I			Polio Virus Type II			Polio Virus Type III		
	Number of children with antibodies	Number of children receiving vaccine	Percent of children with antibodies	Number of children with antibodies	Number of children receiving vaccine	Percent of children with antibodies	Number of children with antibodies	Number of children receiving vaccine	Percent of children with antibodies
2 MONTHS OF AGE									
Oral Vaccine	162	183	88.5	173	186	93.0	133	174	76.4
Injectable Vaccine	203	224	90.6	224	233	96.1	161	214	75.2
4 MONTHS OF AGE									
Oral Vaccine	159	187	85.0	189	194	97.4	158	190	83.2
Injectable Vaccine	210	228	92.1	218	228	95.6	186	225	82.7
6 MONTHS OF AGE									
Oral Vaccine	175	189	92.6	191	192	99.5	181	191	94.8
Injectable Vaccine	234	237	98.7	235	238	98.7	232	235	98.7
18 MONTHS OF AGE									
Oral Vaccine	41	45	91.1	46	46	100.0	45	46	97.8
Injectable Vaccine	39	40	97.5	41	42	97.6	41	42	97.6
20 MONTHS OF AGE									
Oral Vaccine	43	44	97.7	45	45	100.0	45	45	100.0
Injectable Vaccine	41	41	100.0	41	41	100.0	41	41	100.0

None of the differences between the oral and injectable vaccine groups is significant

Table 3

A Comparison of the Serologic Response to Oral and Injectable Trivalent Polio Vaccine

Reciprocal Geometric Mean Titers (in International Units) to Three Types of Wild Polio Virus In Children 2, 4, 6, 18&20 Months of Age

	Polio Virus Type I	Polio Virus Type II	Polio Virus Type III
		2 MONTHS OF AGE	
Oral Vaccine	0.42	1.03	0.31
Injectable Vaccine	0.43	1.13	0.27
		4 MONTHS OF AGE	
Oral Vaccine	0.43	7.90 *	1.87 *
Injectable Vaccine	0.30	0.66	0.34
		6 MONTHS OF AGE	
Oral Vaccine	1.10 *	16.93 *	4.22
Injectable Vaccine	1.90	3.54	4.71
		18 MONTHS OF AGE	
Oral Vaccine	2.31	16.30 *	2.91
Injectable Vaccine	1.53	6.04	2.65
		20 MONTHS OF AGE	
Oral Vaccine	4.74 *	20.35	4.38 *
Injectable Vaccine	11.36	20.40	18.75

* Difference in Reciprocal Geometric meanTiter between Oral and injectable Vaccine Groups significant at $p < 0.01$