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SEROLOGIC RESPONSE TO ORAL POLIO VACCINE AND ENHANCED-POTENCY INACTIVATED POLIO VACCINES

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McBean, A. M. (The Johns Hopkins U. School of Hygiene and Public Health, Baltimore, MD 21205), M. L. Thoms, P. Albrecht, J. C. Cuthie, R. Bernier, and the Field Staff and Coordinating Committee. The serologic response to oral polio vaccine and enhanced-potency inactivated polio vaccines. *Am J Epidemiol* 1988;128:615–28.

In a randomized, controlled trial carried out from November 1980 to July 1983 involving 1,114 infants in Baltimore City and in Baltimore and Prince George's counties, Maryland, the serologic response to three doses of two enhanced-potency inactivated polio vaccines was compared with the response to three doses of oral polio vaccine. The mean ages at vaccination were 2.2, 4.7, and 19.9 months, respectively, for the three doses. Seroconversion after the first dose varied from 35% to 84%, and it was higher after oral polio vaccine than after either of the enhanced-potency inactivated polio vaccines for polioviruses types 2 and 3. Approximately two and one-half and 16 months after the second dose, almost all inactivated polio vaccine recipients had antibodies against all three virus types (98–100%). Fewer oral polio vaccine recipients had detectable antibodies to type 1 (89–92%) and to type 3 (96%). After three doses of vaccine, all children had antibodies against types 2 and 3. Approximately 1% of the inactivated polio vaccine recipients and 3% of the oral polio vaccine recipients lacked antibody to type 1. One or two doses of oral polio vaccine stimulated higher reciprocal geometric mean antibody titers against type 2 poliovirus than did the inactivated polio vaccine. For the other two types, the results were mixed. The third dose of inactivated polio vaccine produced significant increases in the reciprocal geometric mean titers against each of the three poliovirus types and resulted in significantly higher reciprocal geometric mean titers after three doses of vaccine for recipients of inactivated polio vaccine than for recipients of oral polio vaccine.

poliomyelitis; poliovirus; poliovirus vaccine; serology

Since 1962, the Immunization Practices Advisory Committee (1), the Committee on Infectious Diseases of the American Academy of Pediatrics (2), and other groups (3)

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have recommended oral trivalent polio vaccine as the principal polio vaccine for use in the United States. During this time, the annual number of reported paralytic polio cases decreased from 820 cases in 1961 (0.7/100,000) to seven in 1984 (<0.01/100,000) (4), confirming the remarkable effectiveness of this vaccine.

From 1973 through 1984, a total of 138 cases of paralytic polio were reported to the Centers for Disease Control (an average of 11.5 cases per year). One hundred and five of these (76 per cent) were associated with the administration of oral polio vaccine. During the most recent three years for which reporting is complete (1982–1984), 29 cases were reported, and all but one were vaccine-associated. Estimates of the overall risk of paralysis in oral polio vaccine recipients, based on the number of cases of paralytic polio reported in the United States and the number of doses of vaccine administered from 1973 through 1984, are one case per 2.6 million doses distributed, or approximately one case per 500,000 for the first dose given and one case per 13,000,000 for subsequent doses (5).

While the United States has relied almost exclusively on oral polio vaccine for the past 24 years, other countries (Sweden, Finland, and the Netherlands) have achieved control of polio with the use of trivalent inactivated polio vaccine. Prior to the outbreak of nine cases of paralytic polio and one case of aseptic meningitis in Finland in 1984–1985 (6), the circulation of wild poliovirus had not been documented in Sweden and Finland since the early 1960s, and the few cases reported from Sweden and the Netherlands were in immigrants or in people or groups who had refused to be vaccinated (7–9).

The 1984–1985 outbreak in Finland, while raising alarm about the effectiveness of inactivated polio vaccine, was felt to be due to a combination of 1) a decrease in vaccination coverage (the vaccination coverage rate in three-year-old children dropped from 99 per cent to 78 per cent from the 1970s to 1983), 2) antigenic differences between the Finland wild virus strain and the type 3 component of the Finnish inactivated polio vaccine, and 3) low immunogenicity of the type 3 component of the inactivated polio vaccine used in Finland. Finnish authorities continue to express confidence in inactivated polio vaccine, and in 1986 Finland began administering an enhanced-potency inactivated polio vaccine similar to that described below (6).

In the past eight years, new methods have been developed by van Wezel et al. (10) at the Rijks Instituut voor de Volksgezondheid, The Netherlands, for the production of a higher-potency inactivated polio vaccine by means of the microcarrier technique and tertiary monkey kidney cells. Similar vaccines are also made by the Institut Merieux, France, and Connaught Laboratories Ltd., Canada. Salk and colleagues (11–13) have reported excellent antibody responses following one and two doses of this type of vaccine. This paper reports the results of a study that compares the serologic response in healthy American infants given three doses of enhanced-potency inactivated polio vaccine made by the new production methods with the response of children given three doses of commercially available oral polio vaccine.

MATERIALS AND METHODS

Participants and study design

Children aged six through 13 weeks ("two months") attending well-child clinics in Baltimore City and Baltimore County (hereafter called Baltimore) and Prince George's County, Maryland, were enrolled in the study between November 1980 and July 1983. In all cases, parents or guardians were given complete information about the study, and their written informed consent was obtained. In each geographic area (Baltimore or Prince George's County), the children were randomly assigned to receive either oral polio vaccine or one of two enhanced-potency inactivated polio vaccines described below. The children were scheduled to receive additional doses of the same polio vaccine at four and 18 months of age. Diphtheria-tetanus-pertussis vaccine was administered at the same time as the polio vaccine, as was either an oral or injectable placebo corresponding to the kind of polio vaccine that the child did not receive. Blood specimens were obtained at each vaccination and two months after the dose given at four months and at 18 months, that is at ages two, four, six, 18, and 20 months.

Vaccines

Commercially licensed oral polio vaccine manufactured by Lederle Laboratories, Inc. (Wayne, NJ) was used. It contained 800,000 $TCID_{50}$ (tissue culture infectious dose, 50 per cent infectivity) of type 1, 100,000 $TCID_{50}$ of type 2, and 500,000 $TCID_{50}$ of type 3 per 0.5 cm^3 dose. The enhanced-potency inactivated polio vaccines were manufactured by the Institut Merieux, Lyon, France (designated as inactivated polio vaccine A) and by Connaught Laboratories Ltd., Willowdale, Ontario, Canada (designated as inactivated polio vaccine B). Upon receipt of the vaccine in Baltimore and approximately every four months, samples of the enhanced-potency inactivated polio vaccines were sent to the Rijks Instituut, Bilthoven, The Netherlands, where vaccine potency, measured by D-antigen content, was determined by Dr. van Wezel. The range of potency for the Institut Merieux vaccine was 24 to 38, 3.6 to 6.5, and 28 to 36 for types 1, 2, and 3, respectively. The range of potency was 20 to 25, 7.0 to 9.2, and 26

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George's County, Maryland, were enrolled in the study between November 1980 and July 1983. In all cases, parents or guardians were given complete information about the study, and their written informed consent was obtained. In each geographic area (Baltimore or Prince George's County), the children were randomly assigned to receive either oral polio vaccine or one of two enhanced-potency inactivated polio vaccines described below. The children were scheduled to receive additional doses of the same polio vaccine at four and 18 months of age. Diphtheria-tetanus-pertussis vaccine was administered at the same time as the polio vaccine, as was either an oral or injectable placebo corresponding to the kind of polio vaccine that the child did not receive. Blood specimens were obtained at each vaccination and two months after the dose given at four months and at 18 months, that is, at ages two, four, six, 18, and 20 months.

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The diphtheria-tetanus-pertussis vaccine contained 12.5 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, and 4 mouse protective units of pertussis per 0.5 cm^3 dose.

Blood specimens

With Microtainer (Becton-Dickinson, Rutherford, NJ) capillary tubes, approximately 2 cm^3 of blood was obtained by a finger- or heel-stick. After collection, the blood was allowed to clot and was centrifuged. The serum was drawn off, and the serum specimens were refrigerated. They were placed in a freezer and stored at −20 C until examined in the laboratory. Unbiased laboratory analysis was ensured by coding specimens before sending them to the laboratory.

Adverse reactions

At administration of each dose of vaccine, parents were told they would be contacted for the next three days for information on possible adverse local or systemic reactions in their children. They were given a copy of the data form on which the site coordinators would record reaction information on erythema, pain, and induration at the sites of injection, as well as the systemic signs of fever, fussiness, sleepiness, spitting up, decreased eating, increased crying, or seizures. Erythema at the injection site was recorded as present or absent. Pain was rated as "none," "some" (child moved limb or responded negatively when the site was touched), or "much" (child cried when the site was touched). Parents were also instructed in how to take their children's temperatures and were

given a thermometer. When the children returned for a follow-up visit, parents were asked if any severe reactions had occurred since the previous visit.

Laboratory testing

Serum poliovirus-neutralizing antibodies were measured at the Office of Biologics Research and Review, Food and Drug Administration, Department of Health and Human Services (Bethesda, MD), by a sensitive virus cytopathic effect neutralization test in microtiter trays (14). Each day, a serum reference provided by the Rijks Instituut was tested with the experimental sera. This reference was standardized against the World Health Organization International Standard for Antipoliovirus Sera and was assigned values of 11 International Units (IU) of antibody against poliovirus type 1, 50 IU against poliovirus type 2, and 12 IU against poliovirus type 3. A conversion factor was calculated with each test for converting the observed reciprocals of the serum dilution titers to International Units. One International Unit of antibody corresponds to a serum titer of 1:110 for type 1, 1:70 for type 2, and 1:110 for type 3 poliovirus antibody.

RESULTS

Specimens were lost or collection tubes were broken for 20 of 1,134 children enrolled in the study. Of the remaining 1,114 children, 371 received enhanced-potency inactivated polio vaccine A, 366 received oral polio vaccine, and 377 received enhanced-potency inactivated polio vaccine B. In 88 instances, there was not enough serum to perform antibody determinations to all three poliovirus types starting at a dilution of 1:4. Seventy-two of these cases were in infants two months of age. When serum dilutions began at 1:8 or higher for a poliovirus type and no neutralizing activity was found, the data were omitted for that determination, but other serologic data on that child were included in the analysis.

Prevaccination

At enrollment, the percentage of children with antibodies to each of the three poliovirus types was similar for the inactivated polio vaccine A and oral polio vaccine groups (table 1 and figure 1). Approximately 90 per cent had antibodies to type 1, 95 per cent to type 2, and 78 per cent to type 3. More children in the inactivated polio vaccine B group had antibodies to type 2 poliovirus than did children in the oral polio vaccine group and to type 3 poliovirus than did children in either the inactivated polio vaccine A group or the oral polio vaccine group. However, the reciprocal geometric mean titers were similar for all three virus types for each vaccine group (table 2 and figure 2). The differences in the percentage of children with detectable antibodies were probably artifactual and were probably caused by the fact that the inactivated polio vaccine B group children were enrolled later (because enhanced-potency inactivated polio vaccine B was not available at the start of the study). After testing approximately one third of the two-, four-, and six-month blood samples from enhanced-potency inactivated polio vaccine A and oral polio vaccine recipients, we introduced a change in the virus neutralization test that increased its sensitivity approximately threefold (the serum-virus mixtures were incubated overnight at 36 C rather than at 4 C (14)). This explains the higher seropositivity rates in the inactivated polio vaccine B recipients before and after the first dose of vaccine. The change in the antibody technique had no effect, or a minimal effect, on the seropositivity rate at age six months and no effect at 18 or 20 months of age. Modifications in the performance of the neutralization test had no effect on the value of the geometric mean titers, expressed in International Units.

Post first dose

Two and one-half months after the first dose of inactivated polio vaccine, a signifi-

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Age (months) at vaccine grou
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TABLE 1

Percentage of children with detectable antibodies to the three types of wild poliovirus at ages 2, 4, 6, 18, and 20 months, Maryland, 1980–1983

Age (months) at visit and vaccine group*	Mean age (months)	Type 1		Type 2		Type 3	
		No. of children	% with detectable antibodies	No. of children	% with detectable antibodies	No. of children	% with detectable antibodies
Two (prevaccination)							
IPV-A	2.2	331	90.9	338	96.5	318	78.3
OPV	2.2	337	89.6	343	94.2	323	78.0
IPV-B	2.2	332	93.4	351	98.9	317	89.6
Four							
IPV-A	4.6	309	93.5†	311	96.1	306	85.3
OPV	4.7	289	86.5	303	97.7	295	85.4
IPV-B	4.7	312	93.9	324	100.0	311	93.6
Six							
IPV-A	7.0	297	99.0	298	99.0	296	99.0
OPV	7.0	269	92.2	273	99.6	273	96.0
IPV-B	7.1	313	99.0	319	100.0	319	99.7
18							
IPV-A	20.2	225	98.7	229	99.6	228	97.8
OPV	19.8	187	88.8	189	100.0	189	97.4
IPV-B	20.2	245	97.6	247	99.6	247	98.4
20							
IPV-A	22.9	219	99.1	219	100.0	219	100.0
OPV	22.5	192	96.9	193	100.0	193	100.0
IPV-B	22.9	224	100.0	224	100.0	223	100.0

* IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France; OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

† Brackets indicate a difference between the two numbers that is significant at $p < 0.01$.

cant increase in the percentage of children with detectable antibodies was seen only in the inactivated polio vaccine A group and only against type 3 poliovirus, where it increased from 78 per cent to 85 per cent (table 1). Correspondingly, all of the geometric mean titers in the inactivated polio vaccine groups decreased or remained the same compared with the levels seen before vaccination was begun except the titers against type 3 poliovirus for the inactivated polio vaccine A recipients (table 2). After one dose of oral polio vaccine, there was a significant increase from 78 per cent to 85 per cent in the number of children who had detectable antibodies against type 3 poliovirus (table 1). No change was seen for types 1 and 2. Significant increases were seen in the geometric mean titers against types 2 and 3. These geometric mean titers were also statistically greater than the titers obtained after one dose of either of the enhanced-potency inactivated polio vaccines (table 2). For type 1, the geometric mean titer in the oral polio vaccine recipients did not change.

Figure 3 shows the percentage of children who demonstrated seroconversion to each of the vaccines after one dose of vaccine. (Seroconversion is defined as the presence of antibodies four or more times greater than the expected value at the second blood specimen, based on the level of maternal antibodies detected at the first vaccination and their estimated subsequent reduction.) A half-life of 28 days for the maternal antibodies was used in the calculation (15, 16). In general, this meant that children who had an antibody level at the four-month visit that equaled or exceeded the

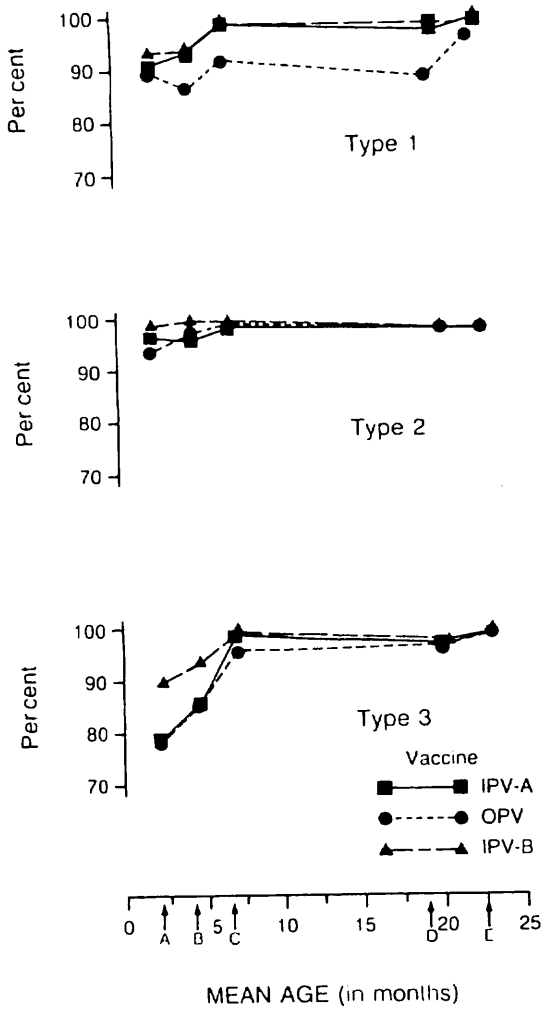

FIGURE 1. Percentage of children with detectable poliovirus-neutralizing antibodies at or after each dose of vaccine for each study group and poliovirus type: Baltimore City and Baltimore and Prince George's counties, Maryland, 1980–1983. *A*, preimmunization titer at age two months; *B*, titer two months post first dose; *C*, titer two months post second dose; *D*, titer at time of third dose; *E*, titer two months post third dose. IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France; OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

titer measured at two months of age were considered to have seroconverted. All three vaccines caused roughly the same amount of seroconversion to type 1 poliovirus (35 per cent to 42 per cent). Oral polio vaccine induced seroconversion to a greater degree than did either of the enhanced-potency inactivated polio vaccines against both type 2 and type 3 (84 per cent and 71 per cent, respectively). However, the enhanced-potency inactivated polio vaccines were able to stimulate seroconversion in a significant number of children in the presence of readily detectable maternal antibodies. For type 2, the range was between 35 per cent and 43 per cent; for type 3, it was between 54 per cent and 61 per cent.

Post second dose

Two and one-half months after receiving the second dose of vaccine, 99 per cent of the enhanced-potency inactivated polio vaccine recipients had detectable antibodies to type 1 poliovirus, while significantly fewer children (92.2 per cent) in the oral polio vaccine group had antibodies to this type. The geometric mean titers for all groups after the second dose of vaccine were significantly greater than they were after one dose. The enhanced-potency inactivated polio vaccine A stimulated the highest titers to type 1 poliovirus.

All three groups had 99 per cent or more children with detectable antibodies to type 2 poliovirus after the second dose of vaccine. The geometric mean titer for the oral polio vaccine group was significantly higher than that for either of the inactivated polio vaccine groups, and the geometric mean titer for the inactivated polio vaccine B group was significantly higher than that for the inactivated polio vaccine A group. The geometric mean titers for all groups were significantly higher than they were after one dose of vaccine.

After the second dose of vaccine, 99 per cent or more of the children in the enhanced-potency inactivated polio vaccine groups had detectable antibodies to type 3 poliovirus compared with 96 per cent for the oral polio vaccine group. The difference was significant between the inactivated polio vaccine B group and the oral polio vaccine group. The geometric mean titers for all groups were significantly greater than they were after one dose of

TABLE 2

Reciprocal geometric mean titers (GMT), in International Units, of antibody to the three types of wild poliovirus in children at ages 2, 4, 6, 18, and 20 months, Maryland, 1980–1983

Age (months) at visit and vaccine group*	Mean age (months)	Type 1		Type 2		Type 3	
		No. of children	GMT	No. of children	GMT	No. of children	GMT
Two							
IPV-A	2.2	331	0.39	338	1.07	318	0.25
OPV	2.2	337	0.38	343	0.92	323	0.25
IPV-B	2.2	332	0.36	351	0.84	317	0.20
Four							
IPV-A	4.6	309	0.28	311	0.64	306	0.32
OPV	4.7	289	0.39	303	7.73	295	1.94
IPV-B	4.7	312	0.17	324	0.60	311	0.20
Six							
IPV-A	7.0	297	2.10	298	3.64	296	4.98
OPV	7.0	269	1.04	273	17.01	273	4.37
IPV-B	7.1	313	1.29	319	6.77	319	3.33
18							
IPV-A	20.2	225	1.37	229	4.43	228	1.78
OPV	19.8	187	0.96	189	9.45	192	2.67
IPV-B	20.2	245	0.51	247	4.21	247	1.35
20							
IPV-A	22.9	219	12.96	219	25.44	219	16.42
OPV	22.5	192	2.69	193	19.20	193	4.41
IPV-B	22.9	224	7.98	224	28.14	223	17.75

* IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France; OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

† Brackets indicate a difference between the two numbers that is significant at $p < 0.01$.

vaccine and were not significantly different from each other.

The percentage of children with antibodies to all the poliovirus types for which their serum was tested was 97 for inactivated polio vaccine A, 90 for oral polio vaccine, and 99 for inactivated polio vaccine B. No child who received inactivated polio vaccine B was seronegative to more than one poliovirus type. One inactivated polio vaccine A recipient lacked antibodies to types 2 and 3. Five oral polio vaccine recipients lacked antibodies to types 1 and 3, and one lacked antibodies to types 2 and 3.

Pre third dose

In the 12- to 13-month interval between the third and fourth blood specimens, there was no statistically significant change in the percentage of children with detectable antibodies, and the geometric mean titers did not drop more than two dilutions.

We examined separately the results from children for whom paired serum specimens were available after the second dose and at the time the third dose of vaccine was given (table 3). The results for these children are essentially the same as those shown in table 2. During this interval, which averaged 13 months, there was less than a one-dilution decrease in the titers in the children who received oral polio vaccine. In the enhanced-potency inactivated polio vaccine groups, the decreases seen in titers were generally greater than for the oral polio vaccine group, but in no case were they more than two serial dilutions.

Post third dose

Two and one-half months after receiving the third dose of vaccine, all children had measurable antibodies against poliovirus types 2 and 3. All children who received enhanced-potency inactivated polio vac-

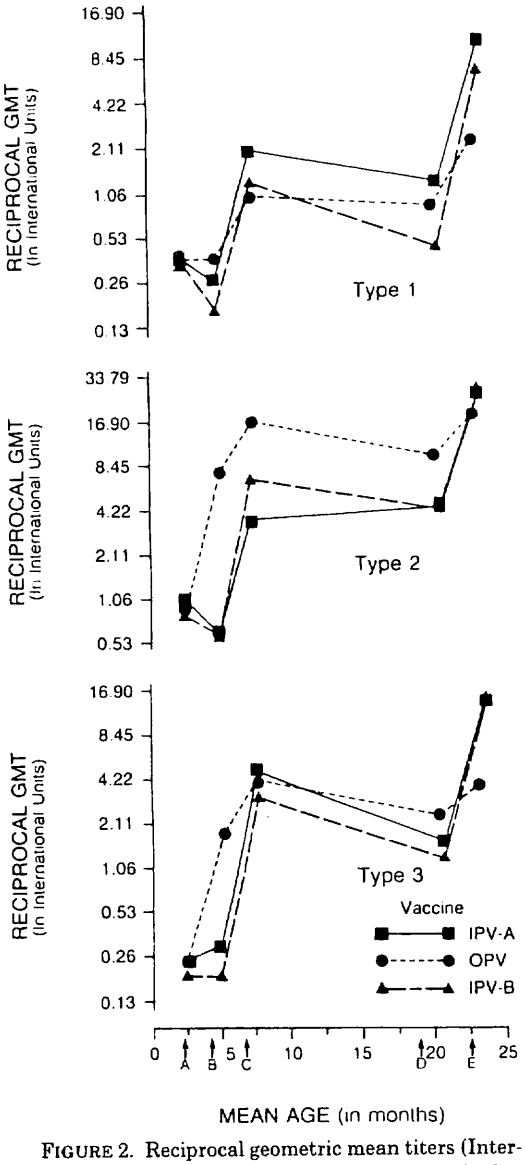

FIGURE 2. Reciprocal geometric mean titers (International Units) of poliovirus-neutralizing antibodies in children at or after each dose of vaccine for each study group and poliovirus type: Baltimore City and Baltimore and Prince George's counties, Maryland, 1980–1983. *A*, preimmunization titer at age two months; *B*, titer two months post first dose; *C*, titer two months post second dose; *D*, titer at time of third dose; *E*, titer two months post third dose. IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France; OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

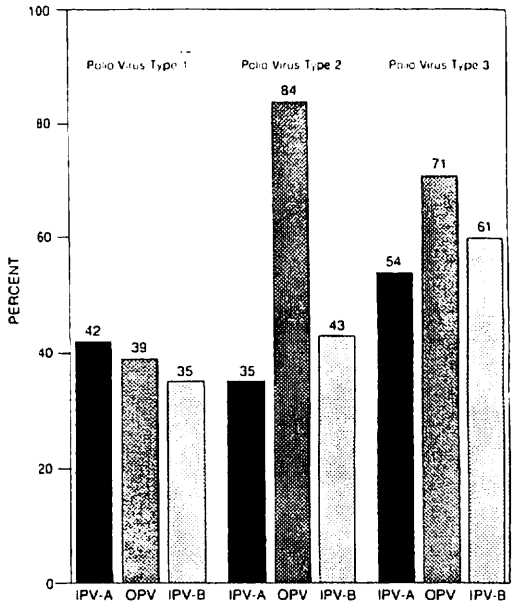

FIGURE 3. Percentage of children with seroconversion to one dose of either inactivated polio vaccine or oral polio vaccine given at two months of age: Baltimore City and Baltimore and Prince George's counties, Maryland, 1980–1983. See text for definition of seroconversion. IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France; OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

cine B were also protected against type 1. Only 1 per cent of the 219 children given three doses of enhanced-potency inactivated polio vaccine A did not produce antibodies to type 1, and only 3 per cent of the oral polio vaccine group did not have measurable antibodies to this type. At a group mean age of 22 or 23 months, the children who received the new enhanced-potency inactivated polio vaccines had significantly higher geometric mean titers to all three poliovirus types than did the children who received oral polio vaccine. The inactivated polio vaccine A group had significantly higher titers for type 1 than did the inactivated polio vaccine B group.

Adverse reactions

Table 4 presents information obtained about adverse reactions that occurred dur-

Reciprocal geom·
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Poliovirus type and vaccine group*	N· child
Type 1	
IPV-A	21
OPV	17
IPV-B	23
Type 2	
IPV-A	21
OPV	17
IPV-B	23
Type 3	
IPV-A	21
OPV	17
IPV-B	23

* IPV-A, trival· polio vaccine pr· France; OPV, triv· valent enhanced-p produced by Conn·

ing the 48 hour vaccines. Pare provide inform less than six, vaccination. A cent) provided time periods. T reports followi first doses of doses, and 544

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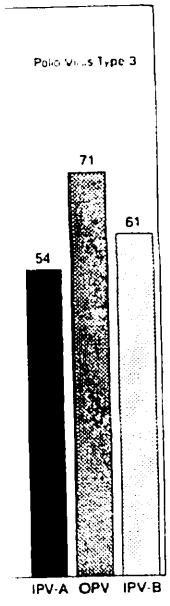

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TABLE 3

Reciprocal geometric mean titers, in International Units, of poliovirus-neutralizing antibodies in children at ages 6 and 18 months for whom both specimens were taken, Maryland, 1980–1983

Poliovirus type and vaccine group*	No. of children	Geometric mean titer		p value
		Age six months	Age 18 months	
Type 1				
IPV-A	215	2.186	1.338	0.0001
OPV	175	1.068	1.027	0.7701
IPV-B	236	1.365	0.527	0.0001
Type 2				
IPV-A	215	3.724	4.416	0.1746
OPV	175	17.744	9.713	0.0001
IPV-B	236	6.855	4.133	0.0001
Type 3				
IPV-A	215	5.021	1.786	0.0001
OPV	175	4.612	2.556	0.0001
IPV-B	236	3.407	1.328	0.0001

* IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France; OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

ing the 48 hours after administration of the vaccines. Parents had the opportunity to provide information for the time periods of less than six, 6–23, and 24–48 hours after vaccination. Almost all parents (95.9 per cent) provided information for all three time periods. The data in table 5 represent reports following the administration of 991 first doses of polio vaccine, 893 second doses, and 544 third doses.

As mentioned above, the study groups were stratified according to geographic area, and the children were then randomized according to the polio vaccine they received. The marked difference in the adverse reaction rates according to the geographic area in which the child lived indicates the importance of the stratification. The reported adverse reaction rates recorded in children from Baltimore are higher for all but one reaction than they are for participants from the Prince George's County Health Department clinics. Interestingly, the only systemic reaction for which there is not a significant difference between the two geographic areas is a temperature ≥39 C, which is the most objective of all the observations ($p > 0.05$).

Comparison of the local reactions (erythema, pain, and induration) to inactivated polio vaccine A and to the injectable placebo given to the oral polio vaccine group for each geographic area shows no statistically significant differences. Likewise, there were no significant differences in any of the systemic reactions. Comparison of these two groups is mentioned first because it is only for these two groups that the infants were truly randomized. As was explained above, inactivated polio vaccine B was not made available for the study until 593 children (53 per cent) had been enrolled in either the inactivated polio vaccine A group or the oral polio vaccine group. Thus, rigorously speaking, the inactivated polio vaccine A and oral polio vaccine groups are historical controls for the inactivated polio vaccine B group. This fact notwithstanding, there were no significant differences between the inactivated polio vaccine B group and the two other groups in the reported rates of local reactions and for four of the six systemic reactions. A greater proportion of the children who received inactivated polio vaccine B were reported to be sleepier than usual, and in Prince George's County, a slightly greater percentage were reported to have a temperature ≥39 C.

Temperatures of >40 C were reported in 12 children. All these episodes occurred during the first 24 hours following vaccination, and they were similarly distributed in the three vaccine groups. One child who received the third dose of oral polio vaccine with the fourth dose of diphtheria-tetanus-pertussis vaccine was reported as having two convulsions within eight hours of receiving the vaccines. This child was seen by a private physician, and no neurologic sequelae were reported after 12 months of follow-up. Thus, we observed one convulsion per 834 fourth doses of diphtheria-tetanus-pertussis vaccine given, or one convulsion per 2,428 doses. No fainting or

TABLE 4

Frequency of reported local adverse reactions in vaccinated children at the site of inactivated polio vaccine or placebo injection and mild systemic reactions reported during the first 48 hours after vaccination, by geographic area and vaccine group per 100 children, Maryland, 1980–1983

	Baltimore				Prince George's County			
	IPV-A*	OPV (IPV placebo)	IPV-B	Total	IPV-A	OPV (IPV placebo)	IPV-B	Total
Number of doses	371	388	352	1,111	459	376	482	1,317
Local reaction								
Erythema	3.2	4.6	5.1	4.3	0.2	0.5	0.4	0.4
Pain								
Some	10.2	13.6	16.2	13.3	1.3	0.5	1.0	1.0
Much	2.7	1.8	1.1	1.9	0.2	0.0	0.0	0.1
Total	12.9	15.4	17.3	15.2	1.5	0.5	1.0	1.1
Induration								
<2 inches	1.1	1.3	2.8	1.7	0.2	0.0	0.0	0.1
2–4 inches	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.1
Systemic reaction								
Temperature ≥39 C	38.5	34.5	31.5	34.9	25.7	29.2	33.8 †	31.8
Sleepier than usual	40.9	36.8	59.9	54.0	5.7	6.6	12.8	8.6
Fussier than usual	63.6	64.0	69.3	63.7	18.9	21.0	26.8	23.4
Spitting up more than usual	8.9	9.2	11.1	11.7	1.3	1.5	<0.1	1.0
Eating less than usual	15.4	14.7	23.8	17.8	2.1	2.1	2.9	2.4
Crying more than usual	28.0	29.4	33.8	27.1	7.2	8.2	5.8	5.8

* IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France; OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

† Brackets indicate a difference between the vaccine groups for each geographic area that is significant at $p < 0.01$.

other neurologic events were reported for any of the children in the three days following vaccination or in the rest of the period between vaccinations.

The rates of local reactions at the site of diphtheria-tetanus-pertussis vaccinations are shown in table 5. Again, there is a marked difference in the rates for each of the two geographic areas. In no case is the rate for children who received enhanced-potency inactivated polio vaccine plus diphtheria-tetanus-pertussis vaccine significantly higher than for the children who received oral polio vaccine plus diphtheria-tetanus-pertussis vaccine.

Potentially confounding factors

Because this study was carried out in the United States, where oral polio vaccine is routinely administered, it is possible that study participants could have been exposed to vaccine virus given to a sibling or other close contact which would have stimulated the production of polio antibodies. This concern was, in part, addressed by the finding that in the 12- to 13-month interval between the third and fourth blood specimens, there was a drop in antibody titers in all three groups against all three virus serotypes except in the inactivated polio vaccine A group, which had a higher, although not statistically greater, type 2 antibody titer at the 18-month visit compared with the six-month visit (tables 2 and 3).

In addition, at each visit, parents were asked about the administration of oral polio vaccine to a sibling or other child living in the same household. Table 6 compares the

TABLE 5

Frequency of local adverse reactions in vaccinated children at the site of diphtheria-tetanus-pertussis (DTP) injection during the first 48 hours after vaccination, by geographic area and vaccine group per 100 children, Maryland, 1980–1983

	Baltimore				Prince George's County			
	IPV-A*	OPV	IPV-B	Total	IPV-A	OPV	IPV-B	Total
Number of doses	371	388	352	1,111	459	376	482	1,317
Local reaction at site of DTP injection								
Erythema	19.2	26.8	23.9	23.4	3.1	3.5	4.3	3.6
Pain								
Some	23.4	38.4	44.9 †	35.5	4.1	5.6	7.9	5.9
Much	10.8	10.3	10.5	10.5	0.2	0.0	0.2	0.2
Total	34.2	48.7	55.4	46.0	4.3	5.6	8.1	6.0
Induration								
<2 inches	22.6	22.9	28.1	24.5	1.5	2.9	4.8	3.1
2–4 inches	1.1	0.5	0.2	0.6	0.2	0.0	0.0	0.1

* IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France; OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

† Brackets indicate a difference between the vaccine groups for each geographic area that is significant at $p < 0.01$.

TABLE 6

Reciprocal geometric mean titers (GMT), in International Units, of poliovirus-neutralizing antibodies in children two months after the third dose of polio vaccine, by whether or not a sibling received oral polio vaccine during the study, Maryland, 1980–1983

Vaccine group* and poliovirus type	GMT if sibling received OPV	GMT if sibling did not receive OPV	*p* value
IPV-A	(n = 54)†	(n = 165)	
1	10.732	13.778	0.2508
2	24.296	25.827	0.6826
3	14.559	17.083	0.4224
OPV	(n = 37)	(n = 156)	
1	1.527	3.081	0.0673
2	13.136	21.015	0.0201
3	3.027	4.826	0.0394
IPV-B	(n = 60)	(n = 164)	
1	9.234	7.564	0.2073
2	31.146	27.120	0.1295
3	20.033	16.975	0.2351

* IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France; OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

† Number of children.

reciprocal geometric mean titers two months after the third dose of vaccine in study participants who had siblings who received oral polio vaccine during the course of the study with those who did not. If the oral polio vaccine had had a contaminating effect, one would expect to see higher titers in the children whose siblings received it. For the children who received inactivated polio vaccine A or oral polio vaccine, the data show the opposite trend. For the inactivated polio vaccine B recipients, the titers are slightly higher for children whose siblings received oral polio vaccine, but the differences are not statistically significant.

DISCUSSION

The results of this study confirm and extend the data presented by Salk (12) and Salk et al. (11) concerning the ability of the new enhanced-potency inactivated polio vaccines to stimulate antibody production in almost all children after two doses of vaccine. The initial report by Salk et al. (11) primarily involved Finnish children in

whom vaccination was begun at five months of age when the level of maternal antibodies would have waned to one eighth the level at two months of age, the age at which children were enrolled in this study. The data presented here demonstrate the ability of one dose of the new enhanced-potency inactivated polio vaccines to stimulate seroconversion in 35 per cent to 61 per cent of these younger children in spite of the higher maternal antibody levels. Although Salk (12) has argued that one dose of the enhanced-potency inactivated polio vaccine is sufficient to provide protection, the data in this study show the impact of the second and third doses of enhanced-potency inactivated polio vaccine. The second dose results in seroconversion in essentially all the enhanced-potency inactivated polio vaccine recipients and provides them with measurable protection against paralytic disease (17). As shown in table 2 and figure 2, the third dose of enhanced-potency inactivated polio vaccine causes a major rise (5.7- to 15.8-fold) in reciprocal geometric mean titers against each of the three poliovirus types. Thus, while the first two doses are important for stimulating detectable antibodies and assuring protection for all children, the third dose stimulates significantly higher antibody titers which are greater than those seen after three doses of oral polio vaccine.

This study has shown the superior ability of oral polio vaccine to induce seroconversion after one dose of vaccine in a population with high levels of maternal antibody. However, it is also clear that the second dose of oral polio vaccine is needed to bring about seroconversion in those who do not respond to the first dose and to enhance the level of antibody among all the recipients. The third dose of oral polio vaccine is important to increase the percentage of children with demonstrable antibodies against type 1 to 97 per cent and to increase the reciprocal geometric mean titer (2.5-fold) against this type. For types 2 and 3, the third dose of oral polio vaccine adds little to the reciprocal geometric mean titer. There is approximately a twofold increase, bringing recipients to about the same level of antibodies they had two and one-half months after the second dose of oral polio vaccine, but it assures measurable protection in all the children (100 per cent have antibodies). Thus, we have reconfirmed the capability of oral polio vaccine to induce excellent levels of protection in almost all children who receive three doses of vaccine (18).

A US immunization program which relies on either oral polio vaccine or enhanced-potency inactivated polio vaccines should require a three-dose schedule during the first 15 to 18 months of life. Although it might be possible to give fewer doses if the first dose were withheld until children were six to seven months of age, we believe that the greatest number of children can be continuously protected by beginning polio immunization in the United States at two months of age, with a second dose at four months of age, as in this trial. Figure 1 shows the excellent situation that exists in the United States. Of those children who receive their first dose of vaccine by age two months, no more than 13.5 per cent are susceptible to type 1 poliovirus, no more than 6 per cent to type 2, and no more than 22 per cent to type 3. Because of the risk of infection with wild virus which still remains, however, susceptibility of the childhood population should not be allowed to drop below these levels by delaying the time at which polio immunization is begun.

The three-dose schedule of enhanced-potency inactivated polio vaccine is important for other elements of immunity conferred by that vaccine. It is well recognized that the lower-potency inactivated polio vaccines were not as efficient as was oral polio vaccine in protecting exposed people from incubating and shedding wild virus (19). In an epidemic in Rhode Island (19), pharyngeal shedding of virus was decreased from 75 per cent to 33 per cent in children with detectable antibody following inactivated polio vaccine administration, but shedding in the stool was decreased only in

those children with high antibody titers (>1:128). Similar data were reported by Glezen et al. (17). They showed that in children vaccinated with inactivated polio vaccine who were given a challenge dose of type 1 oral poliovirus vaccine, the frequency of pharyngeal and fecal shedding was inversely proportional to the level of antibody present at the time of challenge. Thus, three doses of enhanced-potency inactivated polio vaccine would reduce the degree of shedding of virus and of community spread of either wild or vaccine virus to a greater extent than would two doses of enhanced-potency inactivated polio vaccine. Horstmann (20) postulates that the new enhanced-potency inactivated polio vaccines may increase the amount of secretory immune globulin A produced and thus reduce the amount of virus shed more than did the previously used inactivated polio vaccines.

The similarity in the local and systemic reaction rates presented in tables 4 and 5 indicates that the simultaneous administration of inactivated polio vaccine with diphtheria-tetanus-pertussis vaccine does not increase the rate of either local or systemic reactions over the simultaneous administration of oral polio vaccine with diphtheria-tetanus-pertussis vaccine. In addition, fever (temperature ≥39 C) and the mild systemic reactions reported in the oral polio vaccine group are generally similar to or lower than those reported in the literature following the administration of diphtheria-tetanus-pertussis vaccine (21, 22). Two exceptions are "crying more than usual" and "eating less than usual," which are more frequently reported in the Baltimore children in this study. However, the site coordinators asked mothers if their children were "crying more" or "eating less" than usual, not whether they were anorexic or exhibiting high-pitched, inconsolable crying, which are the signs reported in the literature. Thus, the higher rate could be expected.

The potentially confounding role of the spread of oral polio vaccine from a vaccinated sibling was addressed by the data presented in table 6. In addition, Ogra (23) and Dhar and Ogra (24), studying children in groups of six to 12, have shown that a dose of oral polio vaccine given seven months after three doses of the less potent inactivated polio vaccine given at two, three, and four months of age will result in a significantly greater booster effect than that seen with an additional dose of inactivated polio vaccine. Thus, because we did not see higher titers in the enhanced-potency inactivated polio vaccine recipients whose siblings received oral polio vaccine, it is unlikely that the very good response we have ascribed to the new enhanced-potency inactivated polio vaccines is due to contamination and unintentional immunization with oral polio vaccine shed by other children.

The presence of such high titers of antibodies following the three-dose enhanced-potency inactivated polio vaccine schedule used in this study indicates that a change could be made in the current Immunization Practices Advisory Committee recommendation to give three doses of inactivated polio vaccine at two, four, and six months of age, followed by a fourth dose one year later. For vaccines of D-antigen content comparable to those used in this study, two doses of vaccine given in the first year of life, beginning as early as two months of age, followed by a third dose at 15 to 18 months, would be appropriate.

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