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# Research/Recherche

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## Combined immunization of infants with oral and inactivated poliovirus vaccines: results of a randomized trial in the Gambia, Oman, and Thailand

WHO Collaborative Study Group on Oral and Inactivated Poliovirus Vaccines<sup>1</sup>

*To assess an immunization schedule combining oral (OPV) and inactivated poliovirus vaccines (IPV), we conducted a clinical trial in the Gambia, Oman, and Thailand. Children were randomized to receive one of the following schedules: OPV at birth, 6, 10, and 14 weeks of age; OPV at birth followed by both OPV and IPV at 6, 10, and 14 weeks of age; or placebo at birth followed by IPV at 6, 10, and 14 weeks of age. A total of 1685 infants were enrolled; 24-week serum specimens were available for 1291 infants (77%). Across the study sites at 24 weeks of age, the proportion of seropositive children in the combined schedule group was 95–99% for type 1, 99–100% for type 2, and 97–100% for type 3. In the Gambia and Oman, the combined schedule performed significantly better than OPV for type 1 (95–97% versus 88–90%) and type 3 (97–99% versus 72–73%). In the Gambia and Oman, seroprevalences in the IPV group were lower for type 1 (significantly lower in the Gambia); significantly lower for type 2; and significantly higher for type 3, compared with the OPV group. In Thailand, the IPV group had significantly lower proportions of children who were seropositive for each of the three types, compared with the OPV group. The responses to OPV in the Gambia, Oman, and Thailand were consistent with previous studies from these countries. IPV given at 6, 10, and 14 weeks of age provided inadequate serological protection against poliovirus, especially type 1. The combined schedule provided the highest levels of serum antibody response, with mucosal immunity equivalent to that produced by OPV alone.*

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Requests for reprints or copies of the full study report (**WHO Collaborative Study Group on Oral and Inactivated Poliovirus Vaccines. Response to an infant immunization schedule combining oral and inactivated poliovirus vaccines compared with either vaccine alone: results of a randomized trial in the Gambia, Oman, and Thailand.** Unpublished document WHO/VRD/95.1) should be addressed to: Dr Susan E. Robertson, Vaccine Research and Development, Global Programme for Vaccines and Immunization, World Health Organization, 1211 Geneva 27, Switzerland.

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## Introduction

In 1988 the World Health Assembly established the target of global eradication of poliomyelitis by the year 2000 (1). Since then, remarkable progress has occurred in freeing many countries from the disease (2, 3). Extensive use of trivalent oral poliovirus vaccine (OPV) has been associated with interruption of wild poliovirus circulation in the Americas, where the last case of paralytic disease associated with wild poliovirus isolation occurred in August 1991 (4).

Current poliomyelitis eradication strategies recommended by WHO focus on the early and intensive use of OPV with routine delivery of doses at birth, and subsequently at 6, 10, and 14 weeks of age. Also recommended for countries where poliomyelitis is endemic are supplemental OPV delivery strategies, including national immunization days and house-to-house immunization in high-risk areas — strategies that were successful in the elimination effort in the Americas and which are being adopted in other parts of the world.

None the less, in developing countries there is wide variation in the serological response of children to OPV, with the overall levels of seroresponse being less than those seen in industrialized countries. A review of 32 studies in developing countries found that after three doses of OPV, the mean proportion of infants with detectable levels of serum neutralizing antibody was only 73% (range, 36–99%) for type 1; 90% (range, 71–100%) for type 2; and 70% (range, 40–99%) for type 3 (5). Also, a recent large-scale randomized trial in Brazil and the Gambia has confirmed these findings (6). Even after eight OPV doses delivered in mass campaigns, gaps in immunity, as defined by serum antibody levels, persist in some countries, especially for type 3 (7). There is also evidence that OPV may not always succeed in preventing transmission of wild poliovirus, even when vaccine coverage is excellent. Outbreaks of poliomyelitis have occurred in some countries where coverage with three or more doses of OPV has been high, notably in Brazil (8), Bulgaria (9), the Gambia (10), Jordan (11), Israel (12), Malaysia (13, 14), Namibia (15), Oman (16, 17), and Saudi Arabia (18). In these settings, vaccine efficacy has appeared to correlate with seroconversion rates and some children with well-documented immunization histories have contracted paralytic disease.

Some industrialized countries have become poliomyelitis-free through immunization with inactivated poliovirus vaccine (IPV), but this vaccine has not been recommended by WHO for eradication of the disease in developing countries. When given to children in developing countries at intervals of  $\geq 2$  months, starting at 8 weeks of age or older, the serological response to IPV has been excellent, but it is not known how long this protection lasts (19). Because IPV does not produce the high levels of intestinal mucosal immunity observed with OPV, an individual who is protected from paralytic disease by serum antibody may still excrete and transmit poliovirus to others. Moreover, unlike OPV, IPV is a killed vaccine, and cannot spread secondarily to contacts.

A few countries/areas have become poliomyelitis-free using a combination of OPV and IPV, notably Denmark<sup>a</sup> and the Palestinian self-rule areas of Gaza and the West Bank (20). However, these countries/areas use relatively com-

plex schedules that are not completed until the first birthday or older (Table 1). In 1988, the World Health Assembly requested that research be conducted to develop additional poliomyelitis immunization strategies that could accelerate the success of the eradication effort (1). Subsequently the Global Advisory Group of the WHO Expanded Programme on Immunization specifically requested the assessment of a combined poliomyelitis immunization schedule that would be practical to implement in developing countries, because it was expected that such a schedule could provide infants with the beneficial effects of both poliovirus vaccines at an early age (21).

In response to these recommendations, the WHO Collaborative Study Group on Oral and Inactivated Poliovirus Vaccines was formed. This article reports the results of a randomized clinical trial of a combined poliomyelitis immunization schedule carried out in the Gambia, Oman, and Thailand. To provide findings broadly applicable to future policy recommendations, the combined schedule was studied in different regions of the world. The Study Group investigated a simple schedule with *simultaneous* delivery of OPV and IPV at the ages routinely recommended by WHO for immunization in developing countries, with immunization completed before 4 months of age (Table 1). The trial assessed both the serum immune response and the mucosal immune response (as determined by protection on challenge with monovalent type 1 OPV at 6 months of age).

Table 1: Comparison of the combined poliomyelitis immunization schedules used in Denmark and the Palestinian self-rule areas of the West Bank and Gaza, with those used in the present study in the Gambia, Oman, and Thailand

Age (months)	Denmark	West Bank	Gaza	Present study
Birth	—	—	—	OPV <sup>a</sup>
1	—	—	M1-OPV <sup>b</sup>	OPV + IPV <sup>c</sup>
2	—	OPV	OPV + IPV	OPV + IPV
3	—	OPV + IPV	—	OPV + IPV
4	—	—	OPV + IPV	—
5	IPV	OPV + IPV	OPV	—
6	IPV	OPV	—	—
12	—	OPV	OPV	—
15	IPV	—	—	—
24	OPV	—	—	—
36	OPV	—	—	—
48	OPV	—	—	—

<sup>a</sup> Petersen I. Control of poliomyelitis with inactivated and oral vaccines. Paper presented at: *Fifth Meeting of the European Advisory Group on the Expanded Programme on Immunization*, Athens, January 1991. WHO Regional Office for Europe, unpublished document ICP/EPI/026/9.

<sup>a</sup> OPV = oral poliovirus vaccine.

<sup>b</sup> M1-OPV = monovalent type 1 OPV.

<sup>c</sup> IPV = inactivated poliovirus vaccine.

Table 2: Schedules used in the three study groups, by age

Age	Study group: <sup>a</sup>		
	OPV	OPV + IPV	IPV
Birth <sup>b</sup>	OPV	OPV	Placebo
6 weeks	OPV + DPT	OPV + DPT-IPV	Placebo + DPT-IPV
10 weeks	OPV + DPT	OPV + DPT-IPV	Placebo + DPT-IPV
14 weeks	OPV + DPT	OPV + DPT-IPV	Placebo + DPT-IPV
24 weeks	Challenge	Challenge	Challenge

<sup>a</sup> OPV = oral poliovirus vaccine; DPT = diphtheria-pertussis-tetanus vaccine; IPV = inactivated poliovirus vaccine; DPT-IPV = combined DPT and IPV, given as a single injection.

<sup>b</sup> At birth or first contact after birth.

## Materials and methods

### Study subjects

The study was approved by the following: Gambia: Ministry of Public Health and the Ethical Committee of the Medical Research Council (MRC) Laboratories; Oman: Ministry of Health, the National Maternal Child Health Committee and the Maternal Child Health Committee, North Batinah Region; Thailand: Ministry of Public Health and the Ethical Committee, Phramongkutklo College of Medicine; USA: Institutional Review Board, Centers for Disease Control and Prevention (CDC), Atlanta, GA; and Switzerland: Secretariat Committee for Research Involving Human Subjects, World Health Organization, Geneva.

Enrolled in the study were 1685 healthy infants whose parents provided their voluntary and informed consent. These children were free of apparent illness at their initial examination. Children with low birth weight, incapacitating congenital defects, or other major medical conditions were excluded.

In the Gambia, field work was carried out between January 1990 and February 1991. A total of 505 subjects were recruited from the weekly immunization clinic at the health centre, Brikama, a town of population 10000. Although there was no active surveillance for paralytic poliomyelitis in the Gambia, one case was reported in 1990, and a further case in 1991.<sup>b</sup> Neither of these patients lived in Brikama.

In Oman, field work was carried out between October 1990 and April 1992. A total of 630 subjects were recruited from infants born at Sohar Hospital, whose families were residents of one of the 27 vil-

lages of Sohar District (total population, 65535). Since 1989, intensive surveillance for poliomyelitis has been carried out in Oman, with investigation of all cases of acute flaccid paralysis reported among children under 15 years of age (17). No cases caused by wild poliovirus were detected in 1990 or 1992.<sup>b</sup> In 1991, four cases caused by wild type 3 virus were confirmed; all four individuals lived outside the study district. In response, OPV mass campaigns were conducted from April to December 1991 in parts of Oman adjacent to, but not in the study district. After the completion of the study, the OPV mass campaigns were extended into Sohar District.

In Thailand, field work was carried out between June 1991 and July 1992. A total of 550 subjects were recruited from infants born at Phramongkutklo Hospital, Bangkok (population, 8 million). Intensive poliomyelitis surveillance was initiated in Thailand in 1991. Five cases of paralytic poliomyelitis caused by wild poliovirus were reported in Thailand in 1991 and nine cases in 1992.<sup>b</sup> Most of these patients lived in the north-eastern part of the country; no cases were reported from Bangkok.

The study sites in the Gambia and Oman consisted of rural populations of low socioeconomic status, who were mostly illiterate with large extended families. Pit latrines were common in both sites. In the Gambia, water was obtained from community wells, whereas each house in the study district in Oman had a tank of chlorinated water. The study site in Bangkok enrolled families of intermediate socioeconomic status, who were well educated, the majority having only one child, and most living in areas with modern sanitation.

### Study design

Each enrolled child was randomly assigned to one of the three study groups using a computer-generated list. The groups received one of the following schedules: OPV at birth, 6, 10, and 14 weeks of age; OPV at birth followed by both OPV and IPV at 6, 10, and

<sup>b</sup> Expanded Programme on Immunization. *EPI information system*. Unpublished document WHO/EPI/CEIS/95.1, Geneva, World Health Organization, 1995.

14 weeks of age; or placebo at birth followed by IPV at 6, 10, and 14 weeks of age (Table 2). Each 0.1-ml dose of OPV or placebo was administered as two drops into the back of the mouth using the dropper supplied by the manufacturer. Each 0.5-ml dose of diphtheria-pertussis-tetanus (DPT) vaccine or DPT-IPV was administered by intramuscular injection into the lateral thigh. In Oman and Thailand, vaccines were colour coded and investigators and participants remained blind to the vaccine administered; in the Gambia, investigators were not blind to the identity of the study vaccines.

To provide an indirect measure of mucosal protection against type 1 poliovirus, infants were challenged at 24 weeks of age with a  $10^6$  TCID<sub>50</sub> dose of monovalent type 1 OPV. Excretion of type 1 poliovirus at 7 days' post-challenge was interpreted as a nonprotective level of mucosal immunity.

Additional vaccines were administered during the study period, as routinely recommended in each study country. In all three countries, infants received a dose of BCG at the same visit as the birth dose of OPV or placebo. In the Gambia and Oman, hepatitis B vaccine was given simultaneously with some of the study vaccine doses. In all study sites, an infant multivitamin preparation was offered to parents, but it was not administered at the study visits. Also in Thailand, an infant fluoride preparation was offered to parents, but it was not administered at the study visits.

### Vaccines

Trivalent OPV (SmithKline Beecham Biologicals, Rixensart, Belgium) was formulated to contain  $10^6$  TCID<sub>50</sub>,  $10^5$  TCID<sub>50</sub>, and  $10^{5.5}$  TCID<sub>50</sub> of poliovirus types 1, 2, and 3, respectively, per 0.1-ml dose, representing a 10:1:3 ratio of the virus types. The vaccine was stabilized with magnesium chloride and was the same product routinely supplied through UNICEF at the time the study started in January 1990.<sup>c</sup> One lot of trivalent OPV was used in the Gambia and Oman, with a second lot being used in Thailand. A single lot of monovalent type 1 OPV (SmithKline Beecham Biologicals) containing  $10^6$  TCID<sub>50</sub> of poliovirus type 1 was used for the challenge study in all three sites. These vaccines were shipped on dry ice from the manufacturer to the study sites. Vaccine cold chain monitor cards were activated by the manufacturer prior to shipment and remained with

the vaccine during shipment and storage.<sup>d</sup> Vaccines were stored at  $-20^{\circ}\text{C}$ , with the temperature being monitored twice daily.

Potency tests carried out at two WHO Collaborating Centres showed that the mean potency in logTCID<sub>50</sub> units per dose for the first OPV lot were 6.52, 5.50, and 5.93 for poliovirus types 1, 2, and 3, respectively. Mean potency for the second OPV lot was 6.49, 5.25, and 5.68 logTCID<sub>50</sub> units for types 1, 2, and 3, respectively. For both OPV lots there was less than a 0.5 logTCID<sub>50</sub> drop in the titre in the stability test (48 hours at  $37^{\circ}\text{C}$ ) and in field samples of OPV randomly collected from each of the study sites. The mean potency of the challenge OPV was 6.24 logTCID<sub>50</sub> of type 1 virus per dose, with less than a 0.5 logTCID<sub>50</sub> drop in the titre in the stability test and in field samples.

OPV placebo administered to the IPV group at each visit consisted of sterile water in the Gambia and a 1-mol/l aqueous solution of magnesium chloride (the same composition as the OPV stabilizer) in Oman and Thailand.

IPV (Pasteur Mérieux Sérums & Vaccins, Lyon, France) was formulated to contain 40 D antigen units of type 1 (Mahoney), 8 D antigen units of type 2 (MEF1), and 32 D antigen units of type 3 (Saukett) poliovirus strain (this formulation has been termed enhanced-potency IPV, eIPV, or E-IPV). The IPV was combined with alum-adjuvanted DPT vaccine and stabilized with 2-phenoxyethanol. Two lots of IPV were used: one lot in the Gambia throughout the study and in Oman until 4 August 1991; and the second lot in Oman from 5 August 1991 and in Thailand throughout the study. DPT-IPV and DPT vaccines (Pasteur Mérieux Sérums & Vaccins) were supplied in single-dose prefilled syringes and were shipped from the manufacturer to the study site at 2 to  $8^{\circ}\text{C}$  with cold chain monitor cards (to detect exposure to heat) and freeze watch monitors (to detect freezing).<sup>d</sup> These vaccines were stored at 2 to  $8^{\circ}\text{C}$  with both types of temperature monitors. A single cold chain break occurred in Thailand following a weekend thunderstorm, when the temperature of the study vaccine refrigerator reached  $14^{\circ}\text{C}$ , possibly for as long as 48 hours. The manufacturer and independent experts advised that this temperature exposure would not have been sufficient to affect the potency of the IPV.

The potency of the IPV was tested on the bulk product before it had been mixed with DPT vaccine,

<sup>c</sup> In October 1991 the Global Advisory Group of the WHO Expanded Programme on Immunization recommended that a 10:1:6 formulation of OPV be adopted by national immunization programmes (22).

<sup>d</sup> Expanded Programme on Immunization, Programme for Acute Respiratory Infections, Global Blood Safety Initiative, UNICEF/Copenhagen. *Product information sheets*, 10th ed. Unpublished document WHO/UNICEF/EPI.TS/93.1, Geneva, World Health Organization, 1993.

since after mixing it is not possible to test quantitatively the potency of the IPV in the combination (23). Tests conducted by the manufacturer showed that the first IPV lot had 38, 10, and 33D antigen units per dose of poliovirus types 1, 2, and 3, respectively. The second IPV lot had 42, 9, and 34D antigen units per dose of types 1, 2, and 3, respectively. These results were confirmed by two WHO Collaborating Centres. A review of the IPV potency data by an independent expert concluded that the two IPV lots did not have different potencies.

### **Specimen collection**

To assess serum neutralizing antibody titres against poliovirus types 1, 2, and 3, we collected from each infant a 1-ml blood specimen at all sites by fingerstick or venepuncture at 14 and 24 weeks of age. In Oman and Thailand, cord blood specimens were collected to determine maternally derived antibody levels. In Oman, additional blood specimens were obtained at 6 and 10 weeks of age. The serum was separated, stored at  $-20^{\circ}\text{C}$  and shipped by air on dry ice to the Enterovirus Laboratory, CDC, Atlanta, GA, USA, for testing.

Two stool specimens were collected: the first, just prior to delivery of the challenge with type 1 OPV at 24 weeks of age and the second, 7 days' post-challenge. In the Gambia and Oman, stools were collected by parents in containers and transported to the laboratory the same day. Once received, stool specimens were frozen, pending virus isolation studies. In Thailand, rectal stool samples were collected by study physicians using a thin plastic tube (24). The Thai stool specimens were transported in a cold box to the laboratory, where virus isolation studies were begun the same day.

### **Serology**

Each serum specimen was tested for all three poliovirus types in triplicate using a modified microneutralization assay developed by the Enterovirus Laboratory, CDC. This assay has been used at CDC to determine poliovirus antibody titres in numerous developing countries (6, 8, 16, 25, 26). Serial dilutions of serum (from 1:8 to 1:1024) were incubated with 100 TCID<sub>50</sub> of poliovirus types 1, 2, and 3 at  $36^{\circ}\text{C}$  for 3 hours before  $1-2 \times 10^4$  HEP-2 (Cincinnati) cells were added to each well. Prior to December 1991, sera from the Gambia were tested using the same method, except that HeLa cells were used; the transition from HeLa to HEP-2 (Cincinnati) cells was carefully calibrated. The CDC laboratory participated in an international collaborative study of poliovirus neutralizing antibody tests

and results were comparable with those from other laboratories (27).

Serological results were reported as reciprocal titres of the serum dilution that exhibited 50% inhibition. Seroprevalence was defined by the presence of any detectable antibody (titre  $\geq 8$ ); estimates of seroprevalence were based on sera from all infants who had received the vaccines with intervals between doses that fell within the range 22-91 days. Seroconversion was defined as follows: the presence of any detectable antibody (titre  $\geq 8$ ) in an infant who had no measurable antibody in the previous serum specimen; or a  $\geq 4$ -fold rise in antibody titre between the projected residual level of maternally derived antibody and the infant's specimen, assuming that the half-life of maternal antibody is 28 days. Geometric mean titres were calculated for all seropositives; a titre  $>1024$  was taken to be equal to 2048.

### **Virus isolation from challenge stool specimens**

Virus isolation studies were performed at Mahidol University (Thailand), Medical Research Council Laboratories (Gambia), and Ruchill Hospital (Scotland). All laboratories were blind as to the study subjects' identity and vaccination status. The three laboratories followed a standard protocol for poliovirus isolation on HEP-2 (Cincinnati) cells.<sup>e</sup> The Study Group laboratory coordinator visited each laboratory to monitor adherence to the protocol. Poliovirus isolates were typed using reference antisera prepared by the Rijksinstituut voor Volksgezondheid en Milieuhygiene (RIVM), Bilthoven, Netherlands. Non-polio enteroviruses were not typed. A sample of post-challenge stools from all sites reported as containing polioviruses was examined at Ruchill Hospital, Scotland, with Sabin-strain-specific probes using a polymerase chain reaction (PCR) method (28).

### **Statistical methods**

The following tests were used to detect statistically significant differences in baseline characteristics, seroprevalence rates, seroconversion rates, geometric mean titres, and virus excretion rates among the three study groups at each site:  $\chi^2$ -test, Fisher's exact test, Mantel-Haenszel  $\chi^2$  test for linear trend, and Student's *t*-test.

<sup>e</sup> Expanded Programme on Immunization. Manual for the virological investigation of poliomyelitis. Unpublished document WHO/EPI/CDS/POLIO/90.1, Geneva, World Health Organization, 1990.

## Results

### Enrolment and follow-up

A total of 1685 infants (505 in the Gambia; 630 in Oman; and 550 in Thailand) were enrolled. Within each country, there were no significant differences between study groups in terms of the median or mean age at study visits, sex distribution or distribution of weight for age. The median age at the first vaccine dose was 1 day in Oman and Thailand, but 19 days in the Gambia, reflecting the fact that most children in the Gambia are born at home. The median age at the 14-week visit was 112 days in the Gambia, 115 days in Oman, and 100 days in Thailand. The proportion of males was 50% in the Gambia, 53% in Oman, and 50% in Thailand.

Serum specimens taken at 24 weeks were available for analysis for 1291 (77%) infants who had completed the immunization schedule (339 from the Gambia; 546 from Oman, and 406 from Thailand). The reasons for failing to complete the study were as follows: moving away or inconvenience of travelling to the study clinic (141 infants in the Gambia, 4 in Oman, 138 in Thailand); refusal of a parent to allow further blood collection (9 infants in the Gambia, 37 in Oman, 3 in Thailand); withdrawal by study physicians because the infant was ill (9 infants in Oman, 2 in Thailand); immunizations received outside the study clinic (6 infants in Oman); death (2 infants in the Gambia, 4 in Oman); incomplete identification of forms or specimens (2 infants in the Gambia, 11 in Oman); interval between doses >91 days (12 infants

in the Gambia, 2 in Oman, 1 in Thailand); and the interval between doses <22 days (11 infants in Oman).

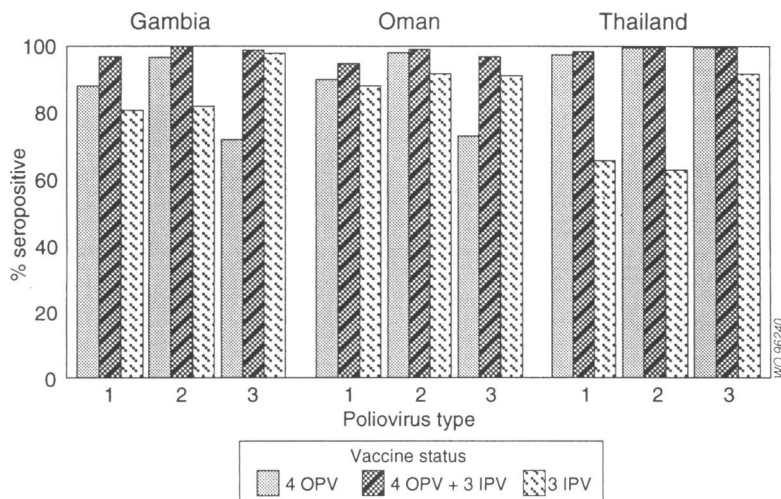
### Seroprevalence

The seroprevalence findings at 24 weeks of age are shown in Fig. 1. In the Gambia, the OPV group seroresponse rates at 24 weeks were 88% for type 1, 97% for type 2, and 72% for type 3. The combined schedule group had seroresponse rates of 97%, 100%, and 99%, respectively, and the corresponding rates in IPV group were 81%, 82%, and 98%. The combined schedule performed significantly better than the referent OPV group for type 1 ( $P < 0.01$ ) and type 3 ( $P < 0.01$ ). The IPV group had seroresponse rates significantly lower than the referent OPV group for type 2 ( $P < 0.01$ ), but significantly higher for type 3 ( $P < 0.01$ ).

In Oman, the OPV group seroresponse rates at 24 weeks were 90% for type 1, 98% for type 2, and 73% for type 3 (Fig. 1). The combined schedule group had corresponding rates of 95%, 99%, and 97%, and the IPV group had rates of 88%, 92%, and 91% for types 1, 2, and 3, respectively. The seroresponse rates were higher in the combined schedule group than in the referent OPV group for type 1 ( $P = 0.05$ ) and type 3 ( $P < 0.01$ ). The IPV group had a significantly lower seroresponse rate than the referent OPV group for type 2 ( $P < 0.05$ ), but a significantly higher response rate for type 3 ( $P < 0.01$ ).

In Thailand, the OPV group seroresponse rates at 24 weeks were 98% for type 1, 100% for type 2, and 100% for type 3, respectively (Fig. 1). The com-

Fig. 1. Seroprevalence to poliovirus types 1, 2, and 3 at 24 weeks of age (10 weeks after last vaccine dose), by vaccination status, in the Gambia, Oman, and Thailand.



bined schedule group had almost identical sero-response rates of 99%, 100%, and 100% for types 1, 2, and 3, respectively. The IPV group had seroresponse rates of 66%, 63%, and 92%, respectively, for types 1, 2, and 3. Rates in the IPV group were significantly lower ( $P < 0.01$ ) than those in the referent OPV group for all three serotypes.

### Seroconversion

Seroconversion rates, by dose, could be calculated for Oman and Thailand.

In Oman, between birth and 14 weeks of age 81%, 97%, and 73%, respectively, of the OPV group seroconverted to poliovirus types 1, 2, and 3 (Table 3). This compares, respectively, with 81%, 99%, and 91% seroconversion rates in the combined schedule group and 71%, 83%, and 81% in the IPV group. The seroconversion rate in the combined schedule group was significantly higher than that in the OPV group for type 3 ( $P < 0.01$ ). The rates in the IPV group were significantly lower than those in the OPV group for type 1 ( $P < 0.05$ ) and type 2 ( $P < 0.01$ ). In Oman, by 24 weeks of age 94%, 99%, and 81% of children in the OPV group; 96%, 99%, and 97% in the combined schedule group; and 90%, 96%, and 95% in the IPV group had seroconverted to poliovirus types 1, 2, and 3, respectively. In Oman, the seroconversion rates by 24 weeks did not differ between groups for types 1 and 2, but for type 3 seroconversion the rates were significantly higher ( $P < 0.01$ ) in the IPV and combined schedule groups than in the OPV group.

In Thailand, between birth and 14 weeks of age, 94%, 99%, and 93% of children in the OPV group; 94%, 99%, and 95% in the combined schedule group; and 40%, 48%, and 79% in the IPV group had seroconverted to poliovirus types 1, 2, and 3, respectively (Table 3). Seroconversion rates were strikingly lower for the IPV group and this difference was significant ( $P < 0.01$ ) for all three types. In Thailand, between birth and 24 weeks of age, the cumulative seroconversion rates were  $\geq 98\%$  for all three types in both the OPV and combined schedule groups. Seroconversion rates for all three types were significantly lower ( $P < 0.01$ ) in the IPV group than in the OPV group, with 67% for type 1, 65% for type 2, and 94% for type 3.

Between countries, the cumulative seroconversion rates by 24 weeks differed for the OPV and IPV groups. The OPV group in Oman had a low rate for type 3 seroconversion and the IPV group in Thailand had low rates for types 1 and 2. In the OPV group in Oman, 94%, 99%, and 81% of children seroconverted to poliovirus types 1, 2, and 3, respectively, after four doses, compared with 98%, 100%, and 100%, respectively, in Thailand. In the IPV group in Oman, 90%, 96%, and 95% of children seroconverted to poliovirus types 1, 2, and 3 after three IPV doses, respectively, compared with 67%, 65%, and 94% in Thailand.

For the combined schedule group, seroconversion rates at 14 weeks were higher in Thailand than in Oman, but by 24 weeks children in both countries showed similar high rates of seroconversion. At 14 weeks (after a total of 5 vaccine doses), 81%, 99%,

Table 3: Cumulative seroconversion rates at 14 and 24 weeks of age to poliovirus types 1, 2, and 3 in infants immunized with OPV alone, OPV + IPV, or IPV alone, in Oman and Thailand

	Seroconversion between birth and 14 weeks:			Seroconversion between birth and 24 weeks:		
	3 OPV	3 OPV + 2 IPV	2 IPV	4 OPV	4 OPV + 3 IPV	3 IPV
<i>Oman:</i>						
Type 1	122/150 (81) <sup>a</sup> referent	112/138 (81) $P = 1.00^b$	96/136 (71) $P = 0.04^b$	141/150 (94) referent	133/138 (96) $P = 0.42^b$	123/136 (90) $P = 0.28^b$
Type 2	145/150 (97) referent	136/138 (99) $P = 0.45^b$	113/136 (83) $P = 0.00^b$	148/150 (99) referent	137/138 (99) $P = 1.00^b$	131/136 (96) $P = 0.26^b$
Type 3	109/150 (73) referent	126/138 (91) $P = 0.00^b$	110/136 (81) $P = 0.12^b$	121/150 (81) referent	134/138 (97) $P = 0.00^b$	129/136 (95) $P = 0.00^b$
<i>Thailand:</i>						
Type 1	117/125 (94) <sup>a</sup> referent	120/128 (94) $P = 1.00^b$	56/141 (40) $P = 0.00^b$	123/125 (98) referent	127/128 (99) $P = 0.62^b$	94/141 (67) $P = 0.00^b$
Type 2	124/125 (99) referent	127/128 (99) $P = 1.00^b$	67/141 (48) $P = 0.00^b$	125/125 (100) referent	127/128 (99) $P = 1.00^b$	92/141 (65) $P = 0.00^b$
Type 3	116/125 (93) referent	121/128 (95) $P = 0.61^b$	111/141 (79) $P = 0.00^b$	125/125 (100) referent	127/128 (99) $P = 1.00^b$	132/141 (94) $P = 0.00^b$

<sup>a</sup> Figures in parentheses are the % of children who seroconverted.

<sup>b</sup> Fisher's exact test compared to the referent (OPV group).

and 91% of children had seroconverted to types 1, 2, and 3, respectively, in Oman, and 94%, 99%, and 95% in Thailand. At 24 weeks, (after a total of 7 vaccine doses), 96%, 99%, and 97% had seroconverted to types 1, 2, and 3, respectively, in Oman, and 99% to all three types in Thailand.

### Geometric mean titres

The geometric mean titres (GMT) at 24 weeks of age and the associated 95% confidence intervals are shown in Table 4.

In the Gambia, the GMTs for poliovirus type 1 were significantly higher in the OPV group (386) and the combined schedule group (418) than in the IPV group (79). For type 2, the GMTs were significantly higher in the OPV group (597) and combined schedule group (744) than in the IPV group (144). For type 3, the GMT was significantly lower in the OPV group (133) than in the IPV group (241) and the combined schedule group (341).

In Oman, the GMTs of neutralizing antibody to type 1 at 24 weeks were not significantly different among the study groups. For type 2, the GMTs in the OPV group (718) and the IPV group (571) had over-

lapping 95% confidence intervals, but the GMT was significantly higher in the combined group (982). For type 3, the GMT was significantly lower in the OPV group (165) and the IPV group (251) than in the combined schedule group (391).

In Thailand, the GMTs for all three serotypes were significantly lower in the IPV group than in the OPV and combined schedule groups.

In both the OPV and the combined schedule groups the GMTs for types 1 and 3 were twice as high in Thailand as in the Gambia and Oman. Type 2 GMTs were similar in the OPV group and the combined schedule group. A different pattern emerged for IPV, with significantly higher GMTs for types 1 and 2 in Oman. The type 1 and 2 GMTs for IPV vaccinees in Oman were 4–5 times higher than those in the Gambia and 8–9 times higher than those in Thailand.

### Influence of maternal antibody on seroconversion in Oman and Thailand

Based on cord blood specimens, maternal antibody levels in Oman and Thailand were classified as high (titre  $\geq 64$ ) or low (titre  $< 64$ ). There was a greater proportion of children with high levels of maternal antibody for all three types in Oman than in Thailand. Among the 619 cord blood specimens from Oman, 62%, 57%, and 32%, respectively, had high antibody titres against poliovirus types 1, 2, and 3. In contrast, among the 411 cord blood specimens from Thailand, 41%, 38%, and 19%, respectively, had high antibody titres against types 1, 2, and 3.

Seroconversion data were stratified according to level of maternal antibody. In the OPV and combined schedule groups in both countries, a high level of maternal antibody had little effect on the seroconversion rate between birth and 24 weeks of age (data not shown). In Oman, the IPV group seroconversion rate was significantly lower for type 1 ( $P < 0.01$ ) and type 3 ( $P < 0.05$ ) in children with high levels of maternal antibody (Fig. 2). In Thailand, the IPV group seroconversion rates were 80%, 80%, and 96%, respectively, against poliovirus types 1, 2, and 3 in children with low levels of maternal antibody, but only 45% ( $P < 0.01$ ), 39% ( $P < 0.01$ ), and 82% ( $P < 0.05$ ), respectively, in children with high levels of maternal antibody.

### Influence of OPV mass campaigns on seroconversion in Oman

Seroconversion data from Oman were stratified to examine the effect of OPV mass campaigns targeted at children aged 0–5 years in 38 districts around the study district. In response to an outbreak of wild type

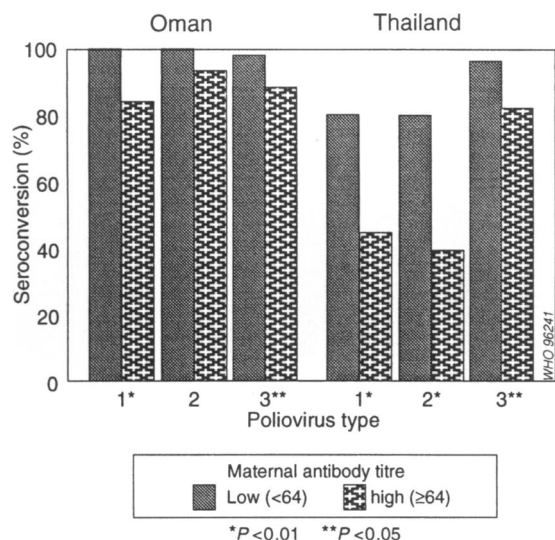
Table 4: Geometric mean titres of serum neutralizing antibodies to poliovirus types 1, 2, and 3 at 24 weeks of age, by study group, in the Gambia, Oman and Thailand

	Geometric mean titre:		
	4 OPV	4 OPV + 3 IPV	3 IPV
<i>Gambia:</i>			
Type 1	386 (297–503)* <i>n</i> = 100	418 (327–533) <i>n</i> = 115	79 (56–113) <i>n</i> = 87
Type 2	597 (492–723) <i>n</i> = 111	744 (642–863) <i>n</i> = 118	144 (103–201) <i>n</i> = 88
Type 3	133 (100–178) <i>n</i> = 82	341 (268–434) <i>n</i> = 117	241 (181–321) <i>n</i> = 105
<i>Oman:</i>			
Type 1	375 (305–460) <i>n</i> = 171	474 (381–589) <i>n</i> = 164	447 (362–550) <i>n</i> = 161
Type 2	718 (620–830) <i>n</i> = 187	982 (888–1085) <i>n</i> = 171	571 (467–697) <i>n</i> = 169
Type 3	165 (132–206) <i>n</i> = 140	391 (325–471) <i>n</i> = 166	251 (197–319) <i>n</i> = 166
<i>Thailand:</i>			
Type 1	681 (559–829) <i>n</i> = 126	840 (728–970) <i>n</i> = 132	49 (36–66) <i>n</i> = 95
Type 2	822 (721–938) <i>n</i> = 128	909 (798–1036) <i>n</i> = 133	68 (48–97) <i>n</i> = 92
Type 3	348 (282–429) <i>n</i> = 128	730 (635–839) <i>n</i> = 133	136 (103–179) <i>n</i> = 134

\* Figures in parentheses are the 95% confidence intervals.



Fig. 2. Seroconversion by 24 weeks of age in children who received inactivated poliovirus vaccine (IPV) at 6, 10, and 14 weeks of age, by level of maternal antibody.



3 poliovirus, mass campaigns were conducted from April to December 1991, but the study district was not included (Fig. 3). At 6 weeks of age, the children in the IPV group had received only placebo, yet 32%, 46%, and 8%, respectively, of those from whom blood samples were drawn after the start of the mass campaigns had seroconverted to types 1, 2, and 3 (Fig. 4). This compared with 10%, 18%, and 8% of children whose blood was drawn before the OPV mass campaigns. These differences were significant ( $P < 0.05$ ) for types 1 and 2. Between birth and 10 weeks of age, these differences were even more striking, with significantly higher ( $P < 0.05$ ) levels of seroconversion for types 1 and 2 in children with secondary exposure to the mass campaign compared with those not exposed (64% versus 27% seroconversion for type 1; 82% versus 41% for type 2) (Fig. 5).

**Challenge virus data**

Challenge virus isolation data were analysed for 1293 (77%) infants (334 in the Gambia; 561 in Oman; and 398 in Thailand). A total of 221 polioviruses were isolated from the 1294 post-challenge stool specimens: 213 type 1; six type 2; and two type 3 polioviruses (Table 5). A PCR test was carried out on 30 of the 221 stools with poliovirus detected by tissue culture methods. These included all type 2 and type 3 isolates, as well as 22 type 1

Fig. 3. Map of Oman showing the study district (Sohar Wilayat) and districts where oral poliovirus vaccine (OPV) mass campaigns were carried out for 0–5-year-olds, April–December 1991.



isolates from all three study countries. The PCR test detected Sabin-strain polioviruses in 29 (97%) of the 30 stools and confirmed the poliovirus type reported. In three stools, two poliovirus types were identified using the Sabin-specific PCR, whereas neutralization

Table 5: Results of studies on post-challenge stool specimens in the Gambia, Oman, and Thailand

Virus isolated:	Gambia		Oman		Thailand	
Poliovirus type 1	31	(9)*	65	(12)	117	(29)
Poliovirus type 2	2	(1)	3	(1)	1	(0)
Poliovirus type 3	0	(0)	1	(0)	1	(0)
Non-polio enterovirus	46	(14)	80	(14)	56	(14)
Toxic specimen	14	(4)	0	(0)	0	(0)
No virus isolated	241	(72)	413 <sup>b</sup>	(73)	223	(56)
<b>Total</b>	<b>334</b>		<b>562</b>		<b>398</b>	

\* Figures in parentheses are percentages.  
<sup>b</sup> One child with <2 days between pre- and post-challenge stool samples was not included in the final analysis.

Fig. 4. Seroconversion to poliovirus types 1, 2, and 3 between birth and 6 weeks among children not exposed or exposed secondarily to oral poliovirus vaccine (OPV) mass campaigns, by vaccine group, Oman.

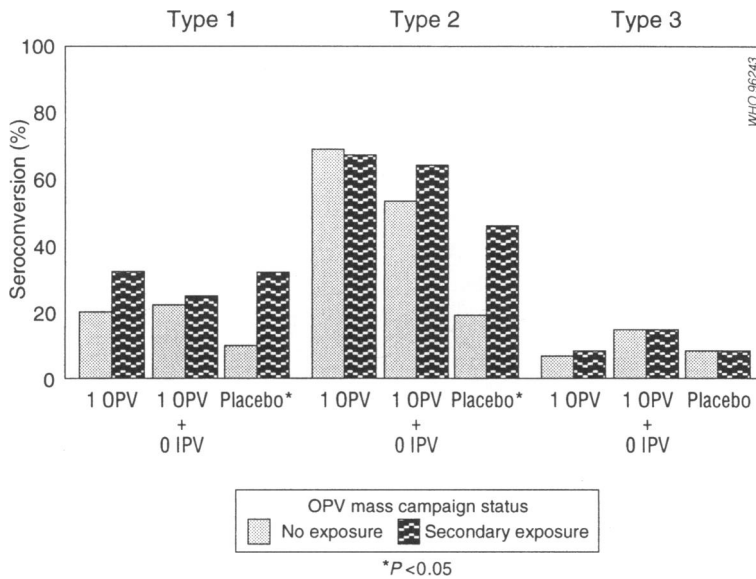


Fig. 5. Seroconversion to poliovirus types 1, 2, and 3 between birth and 10 weeks among children not exposed or exposed secondarily to oral poliovirus vaccine (OPV) mass campaigns, by vaccine group, Oman.

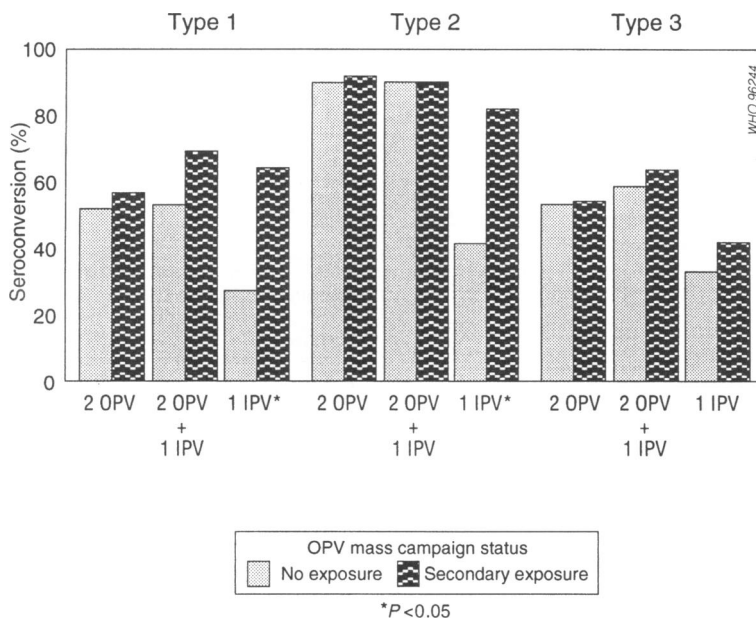
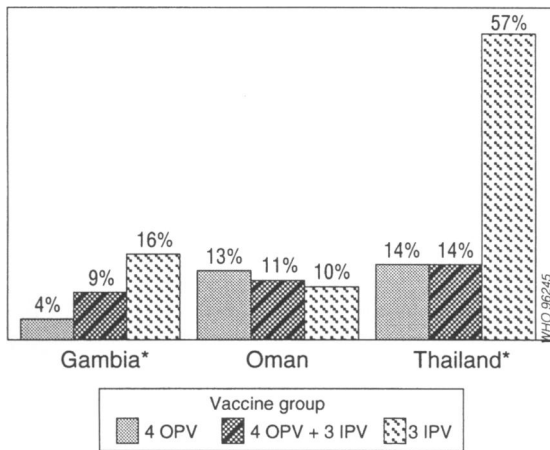


Fig. 6. Proportion of infants shedding poliovirus type 1 in stools one week after challenge with type 1 OPV, by vaccine group, in the Gambia, Oman, and Thailand.



\* Significant difference ( $P < 0.01$ ) between OPV and IPV groups.

tests detected only one type. Non-polio enteroviruses were isolated from 14% of the post-challenge stools in each country, with no difference between study groups at any of the study sites.

In the Gambia, 4% of the OPV group, 9% of the combined schedule group, and 16% of the IPV group shed type 1 poliovirus post-challenge; the difference between the IPV group and the OPV group was significant ( $P < 0.01$ ) (Fig. 6). In Oman, the challenge was administered after mass campaigns with OPV had been initiated in districts surrounding the study site; the rates of shedding type 1 virus did not differ significantly between vaccine groups. In Thailand, 14% of the OPV and combined schedule groups shed type 1 poliovirus post-challenge, compared with 57% of the IPV group; the difference between the IPV and the OPV groups was significant ( $P < 0.01$ ).

## Discussion

The multicentre design of this study permitted determination of responses to three poliomyelitis immunization schedules among children in three developing countries. The combined schedule with simultaneous delivery of OPV and IPV led to excellent serological response in all three countries and levels of mucosal protection similar to those following administration of OPV alone. The combined schedule response was not affected by socioeconomic status or level of maternal antibody. The variable response to OPV was

consistent with previous reports, with lower responses to type 1 and type 3 among children of lower socioeconomic status. As reported previously, high levels of maternal antibody did not affect the response to OPV at 24 weeks. There were strong suggestions of secondary spread of OPV in the mass campaign setting in Oman. The IPV immunization schedule that was used had shorter intervals between doses and an earlier starting age than those used in most previous studies. The serological response to IPV in this abbreviated delivery schedule was lower than that reported in many previous studies, and the response to IPV appeared to be affected by the level of maternal antibody.

## Response to the combined schedule

This study provides unique data on the response of infants to a combined poliomyelitis immunization schedule with administration of OPV at birth and both OPV and IPV at 6, 10, and 14 weeks of age. There was excellent serum antibody response to the combined schedule in all three countries, indicating that such a schedule may provide a means for inducing uniformly high levels of serum antibody with the primary immunization series. The combined schedule using DPT-IPV posed no operational or logistical problems in terms of vaccine delivery: neither extra visits nor extra injections were required. There was no evidence of problems with vaccine safety among the more than 500 children in this study who received the combined schedule. Other implications for global poliomyelitis eradication (e.g., vaccine cost and availability) were not addressed by the present study. More complex combined schedules have been adopted by some countries/areas, including Denmark, Iceland, Israel, Hungary, Lithuania, and the Palestinian self-rule areas of Gaza and the West Bank. Other recent studies in Côte d'Ivoire and the Gambia have examined the effect of giving a single dose of IPV at the same visit as measles vaccine (25, 29). While a schedule with three OPV doses followed by one IPV dose leads to higher levels of seroresponse compared with four OPV doses, the benefit is delayed until 9 months of age. In the combined schedule tested in the current study, all doses of poliovirus vaccine were delivered by 14 weeks (3.5 months) of age.

The combined schedule provided seven doses of poliovirus vaccine, compared with four doses in the OPV schedule and three in the IPV schedule. The response of children at 14 weeks in the combined schedule group after five doses of vaccine (3 OPV + 2 IPV) was superior to that at 24 weeks to four doses of OPV or three doses of IPV. Thus, the combined schedule led to higher antibody titres at an earlier

age with fewer health care contacts. No interference was observed when children received a dose of live vaccine and a dose of killed vaccine at the same visit. The serological response appeared to be as good as that produced by two appropriately spaced doses of either vaccine. The type 1 mucosal protection afforded by the combined schedule was as robust as that achieved with OPV alone.

Although not addressed in this study, an added benefit of the combined schedule might be a lower risk of OPV-associated poliomyelitis among recipients. First, vaccine doses are administered at very young ages, when many infants are still protected by maternal antibody. Second, high levels of serum antibody induced by IPV might prevent some OPV-associated disease in recipients.

### **Response to OPV**

The serological response to OPV in the Gambia and Oman was consistent with that reported in previous studies in these countries (6, 26, 29). After four OPV doses, the proportion of children with antibody titres  $\geq 8$  was low for type 1 (88% in the Gambia; 90% in Oman) and type 3 (72% in the Gambia; 73% in Oman). These results indicate that four doses of OPV cannot be relied upon to provide total immunity to poliomyelitis. Even after four OPV doses, serum antibody gaps remain for type 1 and, especially, for type 3 poliovirus.

There was a much better serological response to OPV in Thailand, with seropositivity rates of 98%, 100%, and 100% for types 1, 2, and 3 after four doses. The response in Thailand resembles that in industrialized countries (5) and that among higher socioeconomic communities in developing countries (26, 30–32). In the present study, children enrolled in Thailand were from urban families of intermediate socioeconomic status, while those in the Gambia and Oman were from rural families of lower socioeconomic status. Socioeconomic status probably reflects critical levels of sanitation, hygiene, and nutrition, and is the best explanation for the higher response to OPV in Thailand. Alternative (though less likely) explanations for the results in Thailand are that they may reflect racial and genetic differences; that Thai children did not receive hepatitis B vaccine during the study (children in the Gambia and Oman did); and that Thai children received infant fluoride supplements (children in the Gambia and Oman did not). Recent malaria studies have demonstrated genetic differences in HLA type and T-cell responses between individuals in the Gambia and Thailand (33, 34). However, the low response to IPV in Thailand does not suggest that humoral immunity to these epitopes was unusually

high. The results of previous studies of simultaneous delivery of hepatitis B vaccine and either OPV or IPV do not suggest that hepatitis B vaccine has any effect on seroresponse to OPV or IPV (35–37). Although fluoride has an adjuvant effect on mucosal immunity in rats, there are no such data suggesting a similar effect in humans (38).

The wild type 3 outbreak of poliomyelitis that occurred during the study in Oman, provided an unexpected opportunity to examine the secondary spread of OPV delivered in mass campaigns. Mass campaigns delivered two doses of OPV to nearly 100% of children aged 0–5 years in 38 districts adjacent to the study district, but not in the study district itself. In the social and cultural setting of Oman, the findings demonstrate that OPV from the mass campaigns penetrated rapidly into the study district. This provides further support for the mass campaign strategy advocated by Sabin et al. (39) and de Quadros et al. (4).

### **Response to IPV**

The overall serological response to IPV was 66–88% for type 1, 63–92% for type 2, and 91–98% for type 3. These findings suggest that IPV as a single vaccine given at 6, 10, and 14 weeks of age provides inadequate serological protection against poliovirus, especially for type 1. These results are consistent with those of several previous studies which showed that delivery of IPV at intervals shorter than 8 weeks led to lower levels of seroresponse and that delivery of the first dose at an early age and high levels of maternal antibody were additional factors leading to lower responses (40, 41).

The response to IPV in the study was highly sensitive to maternal antibody level. There were significantly lower rates of seroconversion for all three poliovirus types in Thailand and for types 1 and 3 in Oman between birth and 24 weeks in children whose baseline maternal antibody titres were  $\geq 64$ . Previous studies have shown that IPV appears to be more sensitive than OPV to the effect of high maternal antibody titres on reducing the neutralizing antibody response to vaccine given in the first months of life (40–44). Krishnan et al. have shown that the negative effect of maternal antibody on response to IPV given at early ages is enhanced if there are shorter intervals between doses; the presence of any maternal antibody before the first IPV dose led to seroconversion rates of 94%, 46%, and 56%, respectively, against poliovirus types 1, 2, and 3 when three IPV doses were given at 4-week intervals, compared with 100%, 97%, and 88%, respectively, when the three doses were given at 8-week intervals (40).

In addition, the present study found site-to-site variation in the response to IPV, which has not previously been reported. Intensive efforts were made to assure that vaccine lot, vaccine stability, and data errors were not the cause of this variation. Once IPV is combined with DPT, it is not possible to use *in-vitro* potency tests. Although *in-vivo* assays could be used, they are relatively imprecise and small differences in potency probably could not be detected. Therefore, we did not examine the potency of IPV field specimens. However, the maintenance of vaccine potency in field samples of OPV from all three study sites is reassuring. Another concern was that two lots of IPV were used in this study: one lot in the Gambia and Oman and another in Oman and Thailand. To assess the potential impact of using different lots, Omani study participants were stratified into two groups, depending on the lot of IPV they received. There were no significant differences in seroprevalence or in seroconversion rates between these groups (data not shown). These findings are consistent with the results of the potency tests on these two lots of IPV. Within the detection limits of currently available tests for IPV potency, there appeared to be no difference between the two lots; however, current methods are not well standardized (23), and a WHO collaborative study to correlate better the findings of *in-vivo* and *in-vitro* potency tests for IPV is in progress (45).

In both the Gambia and Oman, the response of the study children to IPV may have been enhanced by secondary exposure to OPV-related polioviruses shed by other children in the family and the community. In rural Gambia and Oman, families are large and intense social contact is common in the village, at markets, and at health centres. In contrast, infants from intermediate socioeconomic strata in Bangkok are likely to be raised in nuclear families, most often as only children. Thai infants are cared for at home by their mothers or grandmothers, and daycare centres are not available. In Thailand, there was a very low response to IPV for types 1 and 2. Because most of the Thai infants were single children and their lifestyle would not have allowed many opportunities for contact with other OPV-immunized children, the response to IPV in Thailand may possibly be closer to the true response to this vaccine when it is administered over short intervals and at early ages. The effect of schedule and age on response to IPV is demonstrated by the observation that a previous study in Thailand at the same clinic found that 100% of children were seropositive for poliovirus types 1, 2, and 3 after three DPT-IPV doses given at 2-month intervals starting at 8 weeks of age (46).

### Mucosal immunity

The 14% non-polio enterovirus isolation rate in all three virology laboratories involved in the study provides assurance about the sensitivity of virus isolation; isolation rates of  $\geq 10\%$  are considered sufficiently sensitive for the HEp-2 cell line used in this study.<sup>†</sup> In all three study countries, both OPV and the combined schedule provided relatively good mucosal protection, as demonstrated by the low rate of challenge virus excretion.

The low rates at which IPV vaccinees in the Gambia (16%) and Oman (10%) shed type 1 poliovirus after challenge may be due to previous exposure of these children to OPV-related polioviruses shed by siblings or other toddlers. These low rates are consistent with the type 1 serological response among IPV vaccinees (81% in the Gambia and 88% in Oman). In Thailand, the response was very different, with 57% of IPV vaccinees shedding type 1 poliovirus after challenge, which is compatible with the poor serological response to type 1 (66%) in Thai infants immunized with IPV. In Thailand, a high proportion of seropositive IPV vaccinees shed the type 1 challenge virus, whereas this was not true in the Gambia or Oman. This finding suggests that IPV alone may not interrupt transmission of polioviruses, even when individual serological protection has been achieved.

### Conclusions

The variable response to four doses of OPV observed in this study is consistent with previous reports of low response rates to type 1 and especially to type 3 in some developing countries. This finding highlights the need for supplemental OPV delivery strategies to achieve the goal of poliomyelitis eradication. One such supplemental strategy is national immunization days. By the end of 1994, national immunization days had been conducted in 36 countries/areas, with an additional 25 countries planning their first nationwide campaigns in 1995 (47). These mass campaigns are usually targeted at all children less than 5 years of age, and provide two doses of OPV one month apart. Data from the present study in Oman indicate secondary spread of OPV delivered in mass campaigns to young children living in a geographically large "pocket" (a district)

<sup>†</sup> Expanded Programme on Immunization. Laboratory support for activities aimed at the global eradication of poliomyelitis by the year 2000: plan of action. Unpublished document WHO/EPI/GEN/95.4, Geneva, World Health Organization, 1995.

that did not participate in the mass immunization. Another recent study in Cuba found seroconversion among nonvaccinated infants, probably arising from their exposure to vaccine-related polioviruses as a result of OPV mass campaigns (7).

Data from the current study show that a schedule of three doses of IPV at 6, 10, and 14 weeks of age provides inadequate protection against poliovirus. This is probably due to the early starting age, with interference from maternal antibody, and to short intervals between the doses. Other data from this study suggest that IPV alone may not interrupt transmission of polioviruses, as well as not provide uniform individual protection even in fully vaccinated individuals.

In contrast, the combined schedule with simultaneous delivery of OPV and IPV at 6, 10, and 14 weeks of age led to excellent serological response in three different parts of the world. This combined schedule provided levels of mucosal protection comparable to those following administration of OPV alone, and provides a safe and logistically feasible strategy for achieving high levels of serological and mucosal protection in infants at an early age. The response to the combined schedule does not appear to be affected by socioeconomic status or level of maternal antibody. This schedule could be applied routinely or selectively in high-risk areas, including urban slums, locations with poor sanitation, and areas where paralytic poliomyelitis cases continue to occur. Such a schedule offers countries that are well advanced in poliomyelitis eradication an opportunity to close remaining gaps in immunity, an important consideration when wild poliovirus importation will remain a threat until global eradication is achieved.

### Acknowledgements

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### Résumé

#### Vaccination associée des nourrissons par les vaccins antipoliomyélitiques buccal et inactivé: résultats d'un essai randomisé en Gambie, en Oman et en Thaïlande

Le plan mondial d'action pour l'éradication de la poliomyélite, approuvé par l'Assemblée mondiale de la Santé, prévoyait l'évaluation dans les pays en développement d'un schéma vaccinal associant les vaccins antipoliomyélitiques buccal (VPO) et inactivé (VPI). L'OMS a en conséquence organisé un essai clinique collectif en Gambie, en Oman et en Thaïlande. Après tirage au sort, des enfants ont reçu l'un des schémas vaccinaux suivants: VPO à la naissance et à l'âge de 6, 10 et 14 semaines; VPO à la naissance, puis VPO et VPI à l'âge de 6, 10 et 14 semaines; placebo à la naissance, puis VPI à l'âge de 6, 10 et 14 semaines. L'étude avait pour objectifs de déterminer: si l'administration simultanée de VPO et de VPI suivant le calendrier standard produit des réponses en anticorps neutralisants spécifiques de type équivalentes à celles suscitées par le VPI et significativement plus fortes que celles dues au VPO; si trois doses de VPI données à un mois d'intervalle en commençant à l'âge de 6 semaines donnent une réponse en anticorps suffisante contre les trois types de poliovirus; et si le schéma associé VPO/VPI entraîne une immunité au niveau des muqueuses équivalente à celle produite par le VPO et significativement plus forte que celle produite par le VPI. Au total, 1685 nouveau-nés ont été inclus dans l'étude à la naissance; à l'âge de 24 semaines, on disposait d'échantillons de sérum pour 1291 d'entre eux (77%). Pour l'ensemble des trois pays, la proportion d'enfants ayant reçu le schéma vaccinal associé et présentant à l'âge de 24 semaines des titres d'anticorps neutralisants contre le poliovirus  $\geq 8$  était de 95–99% pour le type 1, 99–100% pour le type 2 et 97–100% pour le type 3. En Gambie et en Oman, le schéma associé donnait des résultats significativement meilleurs que le VPO seul pour le type 1 (95–97% contre 88–90%) et le type 3 (97–99% contre 72–73%). Dans ces deux pays, les taux de séroprévalence chez les enfants ayant reçu le VPI étaient plus faibles pour le type 1 (de façon statistiquement significative en Gambie), significativement plus faibles pour le type 2 et significativement plus élevés pour le type 3, par rapport aux enfants ayant reçu le VPO. En Thaïlande, le groupe ayant reçu le VPI comptait une proportion significativement plus faible d'enfants séropositifs pour chaque type, par rapport au groupe ayant reçu le VPO. Les réponses sérologiques au VPO en

Gambie, en Oman et en Thaïlande correspon-  
daient à ce qu'on avait observé lors d'études  
antérieures dans ces mêmes pays. Le VPI ad-  
ministré à 6, 10 et 14 semaines donnait une  
protection sérologique insuffisante contre le polio-  
virus, en particulier de type 1. Le schéma associé  
donnait à la fois les plus forts taux d'anticorps  
sériques et une immunité muqueuse aussi forte  
que celle obtenue avec le VPO.

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