Lessons from Cuba: mass campaign administration of trivalent oral poliovirus vaccine and seroprevalence of poliovirus neutralizing antibodies

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The immunogenicity of trivalent oral poliovirus vaccine (TOPV), which is less effective in tropical than in temperate areas, may potentially be improved in several ways, including increasing the number of doses. Little information is available on TOPV when more than 6 doses are given. The situation in Cuba provides a unique opportunity to relate the seroprevalence of neutralizing antibodies to the dose of TOPV because Cuba has not reported culture-confirmed poliomyelitis since 1973 and TOPV is only administered in twice yearly 1-week mass immunization campaigns. Sera from 2000 children nationwide were studied for neutralizing antibody among children who received 0, 2, 4, 6 and 8 doses of TOPV. These doses were administered in the period 1989–91, when TOPV (from the USSR) was being used with 500 000, 200 000, and 300 000 median tissue-culture-infecting doses (TCID50) for types 1, 2 and 3, respectively—the 5:2:3 formulation. Seroprevalence of neutralizing antibody after two TOPV doses was 91.5% for type 1, 90.8% for type 2, and 45.9% for type 3. Seroprevalence of type-3 neutralizing antibody after 6 doses remained low (73.4%), but increased to 83.5% after 8 doses ($P<0.05$). Although 16.5% of the children remained unprotected for type-3 infection even after 8 doses, mass campaign immunization strategies were sufficient to eradicate the transmission of wild poliovirus in Cuba. Because the seroprevalence of type-1 neutralizing antibody was high (91.5%) after two campaign doses, additional studies using different formulations are needed to determine whether simultaneous improvement in the type-3 response to two campaign doses can be achieved.

Introduction

Although seroprevalence following the administration of trivalent oral poliovirusvaccine (TOPV) approaches 100% in most industrialized countries, only 73% (range, 36–99%) and 70% (range 40–99%) of children in developing countries have detectable antibody to poliovirus types 1 and 3, respectively, after the three-dose standard schedule (*1*). Various factors accounting for these differences are recognized but have not yet been fully elucidated. Approaches such as increasing the number of doses of TOPV, altering the relative components of the trivalent vaccine, using supplemental mass TOPV campaigns, and the combined use of oral and inactivated poliovirus vaccines are currently under review and/or evaluation in field trials by the WHO Expanded Programme on Immunization (EPI).

In Cuba, TOPV is distributed only during two one-week periods each year (February and April), with a two-month interval between them. During these periods, TOPV is given twice to all children aged 0–3 years and once to children at 9 years of age, irrespective of their immunization status (*2*). For the remaining 50 weeks of the year TOPV is not available in the local health units for administration. Between 1970 and 1991, the TOPV that was distributed came from the same source in the USSR. This vaccine had 500 000, 200 000 and 300 000 median tissue-culture-infecting doses ($TCID_{50}$) for poliovirus types 1, 2 and 3, respectively.

Between 1963 and 1973, only 7 virologically confirmed cases of paralytic poliomyelitis were reported. Since 1973 and until the present (August

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Reprint No. **5471**

1993) there has been no evidence of transmission of wild poliovirus in Cuba. Given these conditions, we conducted a study to evaluate the seroprevalence of poliovirus neutralizing antibodies for types 1, 2 and 3 when TOPV was administered by mass campaigns and when >6 doses of TOPV were given.

Methods

Acute flaccid paralysis is a reportable condition in Cuba. All such cases are reported to and investigated by the Ministry of Health.

Of the total population of 10 million people, 2 million live in the capital Havana. Using national census data, a subset of all Cuban children 0–3 years of age was selected by applying stratified random sampling, proportionate to size, by geographic distribution. Children were grouped according to having received 0, 2, 4, 6 or 8 doses of TOPV. The target number to be included in each dose group was 400. Any child born between February and April of any year of the study period was excluded, and only cohorts of children with even numbers of doses were evaluated for seroprevalence. Also excluded were those children whose date of birth was not obtained.

Standard methods were used to measure the serum neutralizing antibody titres.[a] Briefly, this involved testing each serum in the dilution range from 1/8 to 1/1024, using two wells per dilution. The serum/virus mixtures were held at 36 °C for 3 hours before addition of HEp-2 (Cincinnati) cell suspension; tests were read at 5 days. Seroprevalence was expressed as the percentage of children tested who had any detectable antibody. Increases in seroprevalence of type-specific antibodies were consecutively evaluated for statistical significance from one dose group to the next, beginning with the zero dose group.

[a] *Standard procedure for determining immunity to poliovirus using the microneutralization test* (unpublished WHO document WHO/EPI/GEN/93.9, 1993).

Results

Between December 1991 and January 1992 (before the next scheduled TOPV mass immunization campaign in February 1992) 2087 children 0–3 years of age nationwide were bled for sera. After exclusion of children who were born between February and April, or whose birth date was not known, serum samples from 2000 children were tested for neutralizing antibody to poliovirus types 1, 2 and 3. Demographic characteristics and immunization status of these children are listed in Table 1. The total number of children enrolled by age group was similar.

The seroprevalence of neutralizing antibodies to poliovirus type 1 was 91.5% following 2 doses and 96.5% after 4 doses, the percentage increase between these two was statistically significant ($P = 0.05$), but not after 6 or 8 doses where the increase was only small (Table 2). The response to poliovirus type 2 was also significant after 2 and 4 doses, thereafter a small (not significant) increase was observed (Table 2).

The seroprevalence of neutralizing antibodies to poliovirus type 3 after 2 doses was low (45.9%), compared with 91.5% and 90.8% to poliovirus 1 and

Table 1: **TOPV immunization status and demographic characteristics of the surveyed children aged 0–3 years, Cuba, 1992**[a]

No. of doses	Sex		Race[b]			Domicile[c]		Total tested
	Male	Female	White	Mixed	Black	Urban	Rural	
0	196	189	242	79	63	283	100	385
2	206	195	239	107	54	298	103	401
4	213	211	252	105	65	329	94	424
6	191	192	220	91	70	302	81	383
8	227	180	261	74	71	313	93	407
Subtotal	1 033	967	1 214	456	323	1 525	471	2 000
Total	2 000		1 993			1 996		2 000

[a] In Cuba there is a slight excess of males over females and the dominant race is white, followed by mixed and black races. This demographic distribution is represented in the group of children tested in this serosurvey.
[b] The race of 7 children was not given (1 each in the 0-, 2- and 8-dose groups; 2 each in the 4- and 6-dose groups).
[c] Domicile was not given for 4 children (2 in the 0-dose group and 1 each in the 4- and 8-dose groups.)

Table 2: **Percentage of children with antibody to poliovirus types 1, 2 and 3, by the number of TOPV doses administered, Cuba, 1992**

No. of doses	No. of children tested	Percentage with antibody[a]		
		Type 1	Type 2	Type 3
0	385	23.9 (19.6, 28.2)[b]	25.2 (20.8, 29.6)	11.9 (8.6, 15.2)
2	401	*91.5*[c] (88.7, 94.3)	*90.8*[c] (87.9, 93.7)	*45.9*[c] (40.9, 50.9)
4	424	*96.5*[c] (94.6, 98.3)	*97.2*[c] (95.6, 98.8)	*71.2*[c] (66.8, 75.6)
6	383	97.9 (96.4, 99.4)	98.4 (97.1, 99.7)	73.4 (66.9, 77.9)
8	407	98.3 (97.0, 99.6)	98.8 (97.7, 99.9)	*83.5*[c] (79.8, 87.2)
Total	2 000	82.1 (80.4, 83.8)	82.7 (81.0, 84.4)	57.6 (55.4, 59.8)

[a] A titre equal to or greater than 8.
[b] Figures in parentheses indicate the 95% confidence intervals.
[c] Figures in italics indicate a statistically significant increase from the previous dose group.

2, respectively (Table 2). After 4 doses the absolute level for seroprevalence of type-3 neutralizing antibodies remained low (71.2%); however, the increase from 2 doses of TOPV was significant. A 6th dose of TOPV showed a small and insignificant increase in seroprevalence of type-3 neutralizing antibodies, but following 8 doses the increase to 83.5% was statistically significant ($P = 0.01$).

In the zero TOPV dose group there were 385 children who had not yet received any TOPV because they were born after the preceding April immunization campaign. As there has been no detectable circulation of wild poliovirus in Cuba since 1973 and only 7 cases of paralytic poliomyelitis were recorded between 1963 and 1973, it can reasonably be assumed that most of these 385 children acquired their poliovirus immunity from maternal antibodies rather than from wild poliovirus exposure.

Exact age, by month, was available for 381 of the 385 children in the zero dose group. Of the 20 children aged 1 month the percentage with antibody to poliovirus types 1 and 3 was low (55.0% and 30.0%, respectively) (Table 3). By 7 months of age none of the 53 children tested had detectable antibody at a titre of 1/8 to poliovirus types 1 and 3 and only 1.9% had titres ≥1/8 to poliovirus type 2.

By 9 months of age the percentage of children with antibodies to the three poliovirus serotypes increased to 46% for types 1 and 2, and to 17.9% for type 3 (Table 3). Although all these children were born after the last TOPV campaign (in April), the reason for the presence of detectable antibodies may be that they were old enough to have been exposed to vaccinated children who were excreting vaccine-related polioviruses.

Seroprevalence of neutralizing antibodies by the number of TOPV doses was not influenced by sex, race, and urban or rural place of domicile. The only exception to this was that after 2 doses of TOPV, children in rural areas showed a greater response to poliovirus types 1 and 3 ($P < 0.05$).

Discussion

The observed low seroprevalence of type-3 neutralizing antibody may have been due in part to the low titre of the polio-3 component of the USSR-produced TOPV, which was half that recommended by PAHO (300 000 $TCID_{50}$ instead of the EPI/PAHO-recommended titre of 600 000 $TCID_{50}$).[b] However, low seroprevalence of type-3 neutralizing antibody has been observed in several studies in developing countries using routine delivery services, regardless of the dose or formulation used (*1*). To our knowledge, the statistically significant increase in seroprevalence of type-3 neutralizing antibodies from the sixth to the eighth campaign dose has not been observed previously.

Cuba, unlike other countries in the Western Hemisphere, relied solely on twice-yearly mass TOPV immunization campaigns to eradicate the transmission of indigenous wild poliovirus. Despite inherent difficulties with response to the type-3 component by the individuals in this and other studies, the use of mass immunization campaigns in the absence of routine vaccine delivery was sufficient to eradicate poliomyelitis in Cuba (*2, 3*).

Mainland countries in Latin America appear to have eradicated poliomyelitis by supplementing routine immunization services with annual national mass immunization campaigns (*4*). Control of polio-

[b] **Pan American Health Organization.** *Final report: 5th Meeting of the Technical Advisory Group on Polio Eradication in the Americas.* Lima, PAHO, 1988.

Table 3: **Results of testing for antibody to poliovirus types 1, 2 and 3 among 381 unvaccinated children aged 1–9 months, Cuba, 1992**

Age (months)	No. of children tested[b]	Percentage with antibody[a]		
		Type 1	Type 2	Type 3
1	20	55.0 (32.8, 77.2)[c]	65.0 (42.6, 87.4)	30.0 (9.5, 50.5)
2	48	50.0 (35.6, 64.4)	47.9 (33.5, 62.3)	22.9 (10.8, 35.0)
3	46	28.3 (15.0, 41.6)	39.1 (24.7, 53.5)	15.2 (4.6, 25.8)
4	46	26.1 (13.1, 39.1)	21.7 (9.5, 33.9)	8.7 (0.4, 17.0)
5	53	20.7 (9.6, 31.8)	24.5 (12.7, 36.3)	13.2 (3.9, 22.5)
6	50	12.0 (2.8, 21.2)	6.0 (0.0, 12.7)	2.0 (0.0, 6.0)
7	53	0.0 (0.0, 0.0)	1.9 (0.0, 5.7)	0.0 (0.0, 0.0)
8	37	5.4 (0.0, 12.8)	13.5 (2.3, 24.7)	8.1 (0.0, 17.1)
9	28	46.4 (27.6, 65.2)	46.4 (27.6, 65.2)	17.9 (3.4, 32.4)

[a] A titre equal to or greater than 8.
[b] Not included are 4 children whose age in months is not known.
[c] Figures in parentheses indicate the 95% confidence intervals.

myelitis was achieved in tropical areas of the Americas using TOPV with the antigenically poor type-3 component. The use of mass immunization campaigns takes advantage of the community response, not the individual's response, to the rapid exposure of large numbers of children to TOPV (*5, 6*). Flooding communities abruptly with vaccine-related polioviruses by mass immunization of children may quickly induce a sufficient proportion of children to develop the necessary gut immunity to prevent the spread of wild poliovirus.

Children aged 1–9 months who had not yet received TOPV showed a rapid decline in maternal antibody to undetectable levels by 6–7 months of age. The gap in poliomyelitis immunity observed in children aged 6–7 months in Cuba should not be as evident in other countries because of ongoing administration of TOPV through the routine health services.

Overall, the seroprevalence of type-1 neutralizing antibody after three doses of TOPV has been reported in developing countries to be only 73% (range 36–99%) (*1*). In the present study the seroprevalence of type-1 neutralizing antibody after two campaign doses was 91.5%. Perhaps campaign administration of TOPV improves the immunogenicity of specific types of poliovirus. If so, to minimize the "margin of error" attributable to the low antigenicity of the type-3 component of TOPV, it would be highly useful for global eradication efforts to determine, using other vaccine formulations, whether it is possible to improve the immunogenicity of the type-3 component of TOPV simultaneously with the favourable type-1 response to two campaign doses.

Acknowledgements

We thank the staff of all the Cuban health clinics visited for their help in sampling the children enrolled in this study. We acknowledge the financial support given by the Expanded Program on Immunization of the Pan American Health Organization, which is WHO's Regional Office for the Americas in Washington, DC, and by the Expanded Programme on Immunization of WHO, Geneva. In addition, we are grateful to Rosa Palmera for her excellent technical assistance.

Résumé

Les leçons de Cuba: campagne d'administration de masse du vaccin antipoliomyélitique oral trivalent et séroprévalence des anticorps neutralisant les poliovirus

L'immunogénicité du vaccin antipoliomyélitique oral trivalent (PVOT), moins efficace en zone tropicale que sous les climats tempérés, peut être améliorée de plusieurs façons, par exemple en augmentant le nombre de doses. On dispose de peu d'informations sur l'efficacité du PVOT lorsque le nombre de doses est supérieur à six. La situation à Cuba offre une occasion unique d'évaluer la séroprévalence des anticorps neutralisants (AN) en fonction des doses de PVOT, car Cuba n'a pas signalé de cas de poliomyélite confirmés par culture depuis 1973 et le PVOT n'y est administré qu'au cours de campagnes de vaccination de

masse d'une semaine qui ont lieu deux fois par an. La recherche des AN a été faite sur le sérum de 2000 enfants de toutes les régions du pays qui avaient reçu 0, 2, 4, 6 et 8 doses de PVOT au cours de la période 1989–1991. Le vaccin utilisé provenait d'URSS et contenait 500 000, 200 000 et 300 000 DICT (doses infectantes médianes pour les cultures tissulaires) pour les types 1, 2 et 3 respectivement (formule 5:2:3). La séroprévalence des AN après deux doses de PVOT était de 91,5% pour le type 1, 90,8% pour le type 2 et 45,9% pour le type 3. La séroprévalence des AN type 3 était encore faible après 6 doses (73,4%), mais elle atteignait 83,5% après 8 doses (P <0,05). Bien que 16,5% des enfants soient restés sans protection contre l'infection de type 3 après 8 doses, les campagnes de vaccination de masse ont suffi pour mettre fin à la transmission du poliovirus sauvage à Cuba. Etant donné la séroprévalence élevée des AN type 1 (91,5%) après deux doses administrées dans le cadre d'une campagne, il faudrait procéder à des études complémentaires portant sur des formulations différentes afin de déterminer s'il est possible d'améliorer de la même façon la réponse en AN de type 3 à deux doses administrées dans les mêmes conditions.

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