Seroprevalence of anti-polio antibodies in a population 7 months to 39 years of age in Uruguay: Implications for future polio vaccination strategies

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Abstract

This study evaluated the seroprevalence of poliovirus types 1, 2 and 3 antibodies and vaccination coverage in 780 subjects aged between 7 months and 39 years in Montevideo, Uruguay, where oral polio vaccine (OPV) is used. Antibody titers were measured and seroprotection rates and geometric mean titers (GMTs) were compared among four age groups. Vaccination histories were recorded from documents and interviews. Seroprotection rates ranged from 72% to 95% in children aged 7–23 months, 31–77% in 2–9-year olds, 14–45% in 10–19-year olds and 20–59.5% in 20–39-year olds. Seroprotection decreased significantly with increasing age (p < 0.05). Polio vaccination coverage was >90% for the two youngest age groups. These results could help guide public policy decisions regarding polio vaccination, and support the use of inactivated polio vaccine following cessation of OPV.

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1. Introduction

The global use of poliomyelitis vaccines has resulted in near-elimination of this disease [1]. The WHO has declared most regions of the world polio-free [2–4] but poliovirus circulation persists in four countries where the virus remains endemic, and which account for over 90% of the world’s cases [5]. Universal vaccination against poliomyelitis is part of the national schedule in Uruguay beginning with oral polio vaccine (OPV) in 1962 and it is maintained as part of the Expanded Program on Immunization (EPI): children receive a 3-dose primary vaccination series at 2, 4 and 6 months, with one booster at 1 year of age and a second booster at 5 years of age when entering school. This second booster was removed from the schedule in 2001. Vaccination of newborns against poliomyelitis has never been conducted and national immunization days (NID) have never been implemented in the country. OPV is given at the same time as the combined pediatric vaccines [initially a trivalent vaccine [diphtheria, tetanus and pertussis], then a tetravalent vaccine [including Haemophilus influenzae type b] and currently a pentavalent vaccine [including hepatitis B]). This means that vaccination coverage against polio should be similar to that of other routine childhood vaccinations. Indeed, vaccination coverage in Uruguay with three doses of OPV is greater than 90% in children younger than 1 year [6]. The Americas have been free of wild poliovirus since 1989 and the last case of polio in Uruguay caused by wild virus occurred nearly 30 years ago. Moreover, visitors from endemic areas are very infrequent and there are no reports of imported cases. However, two cases of vaccine associated paralytic poliomyelitis (VAPP) have been confirmed [7,8].

In Uruguay, as in other countries, authorities will have to choose between discontinuing polio vaccination altogether or beginning the use of inactivated polio vaccine (IPV) because the risk of VAPP and vaccine-derived polioviruses (VDPV) means that OPV use needs to be stopped [9–11]. Before adopting new strategies it is important to establish the current level of protection in the population and the seroprevalence of antibodies against each of the three vaccine viruses. This study was designed to estimate anti-poliovirus types 1, 2 and 3 antibody seroprevalence in four age groups ranging from 7 months to 39 years of age to provide data to assist those involved in deciding future national polio vaccination strategies.

2. Materials and methods

2.1. Study design

This descriptive, transversal epidemiologic study took place in Montevideo, Uruguay from November 2003 to November 2004. It was conducted according to the Declaration of Helsinki (revised Edinburgh 2000), and all applicable national and international...
guidelines and regulations relating to biomedical investigation. The study protocol was approved by the Ethics Committee of the School of Medicine of the University of the Republic, Montevideo, and it was registered by the Record of Clinical Studies of the Ministry of Public Health of Uruguay.

2.2. Participants and centers

Participants were enrolled at two centers: subjects up to 13 years of age were enrolled at the Pediatric Hospital of Centro Hospitalario Pereira Rossell (PH-CHPR) and subjects between 14 and 39 years old were enrolled at Medilab. PH-CHPR is the national pediatric hospital, providing care to the public sector in Montevideo, which accounts for approximately 30% of all children in Montevideo. It is also the reference hospital for complex cases for the entire country. Medilab is a clinic specialized in occupational medicine, environmental hygiene and industrial safety, which provides health certificates for workers as well as for elite and recreational athletes and school sports team members. The social and cultural characteristics of the subjects covered by these centers are sufficiently representative of the national pattern to allow the results to be generalized to the entire population.

All residents of Montevideo aged between 7 months and 39 years old were eligible for inclusion. Subjects who visited the centers for a blood extraction for reasons not related to the study were invited to take part, and willing participants were consecutively enrolled in this study. Written informed consent was given by all subjects over 18 years of age (>18 years) and by the parents or legal guardian for subjects under 18 years. Adolescents aged from 14 to 17 years old completed an informed consent form in addition to their legal representative. Subjects were excluded if they had a known immune disorder, had been treated with immunodepressant drugs or radiotherapy in the previous 12 months, had received systemic corticoids (enteral or parenteral) for more than 2 weeks in the last 3 months, or at doses ≥1 mg/(kg·day) over several days in the previous month, or had received immunoglobulins or blood transfusion in the last 3 months. On enrollment, subjects were stratified within four age groups: Group 1: 7–23 months; Group 2: 2–9 years; Group 3: 10–19 years; and Group 4: 20–39 years.

A structured questionnaire was used to collect demographic data and vaccination history. Dates of vaccinations against poliomyelitis were obtained from the subject’s certificate of vaccination (CEV) or from Ministry of Health authority databases. The nutritional status of children was evaluated by weight and by comparison with anthropometric scales from the Latin American Centre of Perinatology (CLAP, PAHO/WHO)[12]. Seroprevalence and seroprotection rates of subjects falling in the fifth or lower weight percentile were calculated to evaluate a possible influence of malnutrition.

2.3. Determination of antibody levels

A 2-ml blood sample was collected for the titration of anti-poliovirus antibodies. Sera were prepared at the Central Laboratory of the Ministry of Health within 24 h of drawing. Samples were sent to the virology laboratory of the Faculty of Medicine of Córdoba, Argentina, where the titration of anti-poliovirus antibodies was performed using the WHO standard procedure (WHO/EPI/GEN93.9). The maximum dilution of sera that still protected at least 50% of test cells from viral lysis was determined. Dilutions of 1/8 and higher were considered to be protective. Seroprotection rates (defined as the number and percentage of subjects with titers ≥8 [1/dil]) and geometric mean titers (GMTs) of antibodies were calculated for each serotype in each age group.

2.4. Statistical methods

Assuming a seroprotection rate of 85% for each polio serotype, an estimated 200 subjects were required for each age group to estimate the true seroprevalence rate with a 95% confidence level [±5%]. Since the assumed seroprotection rate in Group 1 is greater than 85%, an estimated sample size of 150 was required for this group for the same confidence level. Children in a weight percentile ≤5 were included and analyzed separately.

Seropositivity/seroprotection rates and anti-polio antibody GMTs were calculated with their 95% CI using exact binomial method (Clopper–Pearson’s method) for each age group. Pair-wise comparisons of percentages of seroprotection among the study groups were conducted by the chi-square test.

3. Results

3.1. Study population

A total of 782 subjects were enrolled, 482 at PH-CHPR and 300 at Medilab. Of these, 150 were between 7 and 23 months (Group 1), 233 between 2 and 9 years (Group 2), 199 between 10 and 19 years (Group 3) and 200 between 20 and 39 years of age (Group 4). Three participants were excluded from the analyses (see Table 1). The demographic characteristics of the study population are summarized in Table 2. There were approximately equal numbers of males and females in each group. Mean ages were 1.18 years, 6.05 years, 15.54 years and 27.53 years in Groups 1 through 4, respectively. Of the 149 children aged 7–23 months and 232 children aged 2–9 years, 37 (24.8%) and 32 (13.8%), respectively, presented in a weight percentile ≤5 (Table 2).

3.2. Antibody prevalence and seroprotection rates

Seroprotection rates and GMT of anti-poliovirus antibodies for each age group are summarized in Fig. 1 and Table 3. Overall, only 161 subjects (20.7%) were seroprotected against all 3 poliovirus serotypes. This included 92 (61.7%) subjects in Group 1, 43 (20.3%) in Group 2, 10 (5.0%) in Group 3 and 12 (6.0%) in Group 4. Among the 780 subjects evaluated, 335 (42.9%) were seroprotected against poliovirus type 1, 528 (67.7%) against type 2 and 245 (31.5%) against type 3.

| Table 1
| Distribution of study population by center and by age. |
|----------------------------------|----------------|----------------|----------------|----------------|----------------|
|                                | Group 1 7–23 months | Group 2 2–9 years | Group 3 10–19 years | Group 4 20–39 years | Total         |
| Center 1                       | 150              | 233             | 99             | –              | 482           |
| Center 2                       | –                | 232             | 199            | 200            | 300           |
| Total                          | 150              | 232             | 199            | 200 (3)        | 782           |
| Evaluable participants         | 149 (1)          | 232 (2)         | 199            | 200            | 780           |

1 person was not evaluated because of not fulfilling the inclusion criterion.
1 person was not evaluated in 3 serotypes for insufficient sample
Serotype 3 was not evaluated in 1 person for insufficient sample.
Table 2
Demographic characteristics of the study population.

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>7–23 months</td>
<td>2–9 years</td>
<td>10–19 years</td>
<td>20–39 years</td>
<td></td>
</tr>
<tr>
<td>n included</td>
<td>149</td>
<td>232</td>
<td>199</td>
<td>200</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male: n (%)</td>
<td>76 (51.0)</td>
<td>120 (51.7)</td>
<td>101 (50.8)</td>
<td>100 (50)</td>
</tr>
<tr>
<td>Female: n (%)</td>
<td>73 (49.0)</td>
<td>112 (48.3)</td>
<td>98 (49.2)</td>
<td>100 (50)</td>
</tr>
<tr>
<td>Male/female</td>
<td>1.04</td>
<td>1.07</td>
<td>1.03</td>
<td>1.00</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.18 ± 0.37</td>
<td>6.05 ± 2.44</td>
<td>15.54 ± 3.29</td>
<td>27.53 ± 4.91</td>
</tr>
<tr>
<td>Range</td>
<td>0.58; 2.00</td>
<td>2.03; 9.98</td>
<td>10.01; 19.96</td>
<td>20.04; 39.98</td>
</tr>
<tr>
<td>Median</td>
<td>1.15</td>
<td>6.01</td>
<td>15.21</td>
<td>26.99</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>9.24 ± 1.59</td>
<td>21.81 ± 9.33</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Range</td>
<td>6.00; 14.50</td>
<td>8.10; 61.00</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Median</td>
<td>9.0</td>
<td>19.9</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;Percentile 5 n (%)</td>
<td>112 (75.2)</td>
<td>200 (86.2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>≤Percentile 5 n (%)</td>
<td>37 (24.8)</td>
<td>32 (13.8)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Not applicable

Fig. 1. Seroprotection rates for anti-poliovirus antibodies 1, 2 and 3 in each age group and overall (between-group differences in seroprotection rates for each poliovirus type are significant (p < 0.001 to p = 0.007) except poliovirus types 1 and 3 in Groups 3 versus 4).

The highest seroprotection rate for type 1 poliovirus was observed in Group 1, and was significantly higher than the rates observed in the other three age groups (p < 0.001 by pair analysis). The seroprotection rate for type 1 poliovirus in Group 2 (112/232 [48.3%]) was also significantly higher than in Groups 3 and 4 (p < 0.001), which were not significantly different to each other (p = 0.590). For poliovirus type 2, the seroprotection rate was highest in Group 1. Again, this was significantly higher than the other three age groups (p < 0.001). Seroprotection for type 2 poliovirus was significantly higher in Group 2, than in Groups 3 and 4 (p < 0.001), and the difference in seroprotection between Groups 3 and 4 was significant (p = 0.003). For poliovirus type 3, the seroprotection rate was significantly higher in Group 1 compared to the other three groups (p < 0.001). The seroprevalence rate in Group 2 was significantly higher than in Groups 3 (p < 0.001) and 4 (p = 0.007).

3.3. Children with weight below the 5th percentile

Among the 381 subjects in the study who were under 9 years of age (Groups 1 and 2), 69 (18%) were at or below the 5th weight percentile; 37 in Group 1 (24.8%) and 32 in Group 2 (13.8%). No statistically significant differences in seroprotection rates were observed between these subjects and those in weight percentiles >5 except for poliovirus type 1 in Group 2: 45.5% for those in percentile >5 (91/200) versus 66% (21/32) (p = 0.034) for those in percentile ≤5 (Fig. 2).

3.4. Vaccination coverage

Documented polio vaccination history (complete/incomplete or booster) was available for 615 of the 780 study participants (78.8%) (see Table 4). Primary vaccination against polio had been completed by 581 subjects (74.5%), although for 31 (4.0%), only the 12-month booster was documented so complete vaccination was classified as

Table 3
GMT of anti-poliovirus antibodies by age group.

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>7–23 months</td>
<td>2–9 years</td>
<td>10–19 years</td>
<td>20–39 years</td>
<td></td>
</tr>
<tr>
<td>Anti-poliovirus type 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n analyzed</td>
<td>149</td>
<td>232</td>
<td>199</td>
<td>200</td>
</tr>
<tr>
<td>GMT (95% CI)</td>
<td>281.5 (214.9; 365.0)</td>
<td>72.2 (58.6; 88.2)</td>
<td>33.1 (27.7; 40.0)</td>
<td>34.5 (28.8; 41.3)</td>
</tr>
<tr>
<td>n (%) GMT ≥ 8 (1/dil)</td>
<td>118 (79.2)</td>
<td>112 (48.3)</td>
<td>50 (25.1)</td>
<td>55 (27.5)</td>
</tr>
<tr>
<td>Anti-poliovirus type 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n analyzed</td>
<td>149</td>
<td>232</td>
<td>199</td>
<td>200</td>
</tr>
<tr>
<td>GMT (95% CI)</td>
<td>845.56 (658.5; 1075)</td>
<td>223.6 (184.9; 270.4)</td>
<td>83.10 (67.36; 102.5)</td>
<td>89 (44.7)</td>
</tr>
<tr>
<td>n (%) GMT ≥ 8 (1/dil)</td>
<td>122 (79.2)</td>
<td>112 (48.3)</td>
<td>50 (25.1)</td>
<td>55 (27.5)</td>
</tr>
<tr>
<td>Anti-poliovirus type 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n analyzed</td>
<td>149</td>
<td>232</td>
<td>199</td>
<td>200</td>
</tr>
<tr>
<td>GMT (95% CI)</td>
<td>164.0 (127.7; 210.6)</td>
<td>34.12 (27.66; 41.68)</td>
<td>17.99 (14.88; 21.76)</td>
<td>21.98 (18.17; 26.31)</td>
</tr>
<tr>
<td>n (%) GMT ≥ 8 (1/dil)</td>
<td>107 (71.8)</td>
<td>72 (31.0)</td>
<td>27 (13.6)</td>
<td>39 (19.6)</td>
</tr>
</tbody>
</table>
Table 4
Vaccination coverage for poliomyelitis and DTP (trivalent) vaccines.

<table>
<thead>
<tr>
<th>Group</th>
<th>7–23 months</th>
<th>2–9 years</th>
<th>10–19 years</th>
<th>20–39 years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n analyzed</td>
<td>149</td>
<td>232</td>
<td>199</td>
<td>200</td>
<td>780</td>
</tr>
</tbody>
</table>

**Polio vaccination % (n)**

- Completed and documented: 87.2 (130) 93.1 (216) 83.9 (167) 18.5 (37) 70.5 (550)
- Not completed and documented: 12.1 (18) 1.7 (4) 0.0 (0) 3.0 (6) 3.6 (28)
- Probable (booster documented): 0.0 (0) 0.0 (0) 3.0 (6) 12.5 (25) 4.0 (31)
- No primary vaccination: 0.0 (0) 0.0 (0) 0.0 (0) 3.0 (6) 0.8 (6)
- History of vaccination not documented: 0.0 (0) 5.2 (12) 6.5 (13) 23.5 (47) 92.7 (72)
- No documents and no recall: 0.7 (1) 0.0 (0) 6.5 (13) 39.5 (79) 11.9 (93)

**DTP (trivalent) vaccination % (n)**

- Completed and documented: 87.9 (131) 92.7 (215) 83.9 (167) 12.0 (24) 68.8 (537)
- Not completed and documented: 11.4 (17) 1.7 (4) 0.5 (1) 3.0 (6) 3.6 (28)
- Probable (booster documented): 0.0 (0) 0.4 (1) 1.5 (3) 2.5 (5) 1.2 (9)
- No primary vaccination: 0.0 (0) 0.0 (0) 1.0 (2) 20.0 (40) 5.4 (42)
- Not documented: 0.0 (0) 5.2 (12) 6.5 (13) 16.5 (33) 7.4 (58)
- Not documented and no recall: 0.7 (1) 0.0 (0) 6.5 (13) 46.0 (92) 13.6 (106)

### 4. Discussion

This study was the first in Uruguay to document the seroprevalence of antibodies against the 3 poliovirus types and the vaccination coverage in the same population. The study design allows the level of protection to be determined in a population in which only OPV has been used and in which the vaccination coverage is known. It is thus possible to relate immunity within the population to the existing vaccination program and identify potentially susceptible groups in the population.

The highest seroprotection rates and GMTs in each age group were for serotype 2 and the lowest for serotype 3. Antibody prevalence against all serotypes decreased significantly with increasing age until at least 20 years of age. Seroprotection rates and GMTs were low in both adolescents and adults, but the differences between those two age groups were not significant. Therefore, older age groups would appear to be at greater risk of infection in the case of the importation of wild virus or the circulation of VDPV [13]. Poliomyelitis is known to occur in adults in countries with wild virus circulation e.g. Namibia in 2006 [14]. A similar study in Argentina also found that seroprotection rates above 90% persisted for at least 6 years following primary and booster vaccination with 4 or 5 doses of OPV, but that seroprotection rates and GMTs were significantly lower at 9–17 years of age; 84%, 90% and 76% for types 1, 2 and 3, respectively [15]. Older age groups were not studied.

The data on antibody prevalence in Uruguay are consistent with that from a number of other countries, including the United States [16], Italy [17–20], Belgium [21], Greece [22], Finland [23] and South Africa [24] indicating that the decline in seroprevalence is primarily associated with the time since the last polio vaccination, and with the lowest seroprotection rates and GMTs occurring in adolescents and young adults. With the exception of Finland, where IPV has been exclusively used since 1960, the data come from populations receiving OPV. As in our study, these studies showed the greatest declines in seroprevalence against poliovirus types 3 and 1. When evaluated, most but not all previously vaccinated individuals with no detectable anti-poliovirus antibodies responded to a booster vaccination [24]. These results therefore indicate that the cessation of OPV without switching to IPV would result in an increasing population of unvaccinated young people at risk of infection from VDPV, imported wild poliovirus, or accidental or deliberate release of poliovirus. A second population, including previously vaccinated individuals, would also be at risk because their immunity had waned. Consequently, the clear demonstration of waning immunity among people vaccinated years earlier will be useful in developing future vaccination strategies, specifically in deciding whether to add IPV to the vaccination schedule following OPV cessation. One must also consider that four countries were polio-endemic in 2008: India, Nigeria, Pakistan and Afghanistan. In these countries, wild poliovirus transmission has not yet been interrupted and together they represent the only known remaining reservoir, with risk of transmission to regions currently free of wild polio infection [5,25,26].

Uruguay experienced an economic crisis from 2000 to 2005, with increased poverty and social exclusion. Body weight is an indicator of nutritional state and protein/calorie malnutrition can result in a functional deficit in T cells and in the complement system [27], which in turn has the potential to reduce immunologic response to vaccination. The economic crisis with increasing malnutrition...
and doubts about the subsequent immunologic response to OPV vaccine in malnourished children, led us to analyze children in the fifth or lower weight percentile separately in case there was an influence on the results. We did not find significant differences in response in children related to weight percentile except for one case where seroprotection was higher in those ≤5. However, others have previously shown a relationship between vaccine response and nutritional state [28,29].

In our study population, vaccination coverage in children was high. More than 95% of children between 7 and 23 months and nearly 95% of those aged 2–9 years had received the primary vaccination series to some extent. This estimate is consistent with data from the national computerized system used to track EPI vaccinations [6] and with the WHO estimated coverage for both three doses of OPV and of DTP vaccine in Uruguay in 2006 [30]. Maintaining poliomyelitis vaccination coverage over 90%, surveillance of acute flaccid paralysis (AFP), maintaining a minimum and controlled stock of virus in laboratories in order to prevent breakdowns and environmental surveillance are essential strategies of the “End Game” for achieving polio disease eradication [11,25,26].

Circulation of VDPV will remain a significant risk after eradication of wild poliovirus [9,11]. Once the final poliomyelitis case caused by wild virus is confirmed and OPV use is stopped, each country will need to decide whether or not to continue polio vaccination with IPV [9]. IPV carries no risk of VAPP or VDPV and it has been shown to be highly immunogenic in studies conducted in Latin America [31–34]. The experience of Canada, the USA and many European countries that have used IPV to achieve or maintain polio-free status with no reported cases of VAPP has recently been reviewed [35]. Mexico switched to IPV in 2007 [36]. Uruguay has been polio-free for nearly 30 years, and OPV is the only vaccine used in the national program. Local decisions on the design and timing of new polio vaccination strategies in Latin America and elsewhere will be aided by the availability of both antibody seroprevalence data against each poliomyelitis virus type and vaccination coverage rates provided by this study.

This study demonstrates that seroprotection declines with age. High vaccination coverage in the first years of life and subsequent high immunologic response against the vaccine serotypes lead to high levels of protection in younger age groups. However, without booster vaccinations, waning immunity leads to vulnerable populations of adults and adolescents. Taking into account the high vaccination coverage for DTP and OPV in Uruguay, various epidemiologic aspects of the disease, the geographic location of Uruguay, and a need to stop using OPV if polio is to be eradicated, the question arises if it is still necessary to continue to expose children and adults to the risks of VAPP and VDPV, for which OPV is the unique source of exposure. IPV is a safe and efficient alternative with the unique source of the ethical implications associated with cessation of polio vaccination altogether.

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