Achieving high immunogenicity against poliovirus with fractional doses of inactivated poliovirus vaccine in Ecuador—results from a cross-sectional serological survey

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Summary

Background In January 2018, Ecuador changed its routine immunization schedule by replacing one full dose of inactivated poliovirus vaccine (IPV) administered intramuscularly at 2 months of age with two doses of fractional IPV (1/5th of full dose, fIPV) administered intradermally at 2 and 4 months of age; and bivalent oral poliovirus vaccine (serotypes 1 and 3, bOPV) continues to be used. We compared seroprevalence and titres of polio antibodies achieved by the past and the current immunization schedules.

Methods This was a cross-sectional serological survey in children in Ecuador who received bOPV and either one IPV dose in 2017 or two fIPV doses in 2018. One blood sample was collected between October 2020 and March 2021 and analysed for presence of poliovirus neutralizing antibodies at CDC, Atlanta by microneutralization assay.

Findings We obtained 321 analysable samples from 329 (97.6%) enrolled children (160 received IPV and 161 fIPV). For serotype 2, seroprevalence was 50.0% (CI95% = 44.2–53.8%) for IPV and 83.2% (CI95% = 78.5–87.1%) for fIPV recipients (p < 0.001). Median antibody titers for serotype 2 were significantly lower for IPV than for fIPV recipients (3.0, CI95% = 3.0–3.5 vs. 4.8, CI95% = 4.5–5.2, p < 0.001). Seroprevalence for serotypes 1 and 3 was above 90% and was not significantly different between IPV and fIPV recipients.

Interpretation Ecuador achieved significantly better poliovirus serotype 2 immunogenicity with two fIPV doses than with one IPV dose, while preserving vaccine supply and reducing costs. Our data provide further evidence that fIPV is a beneficial and potentially a cost-effective option in polio immunization.

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Keywords: Poliomyelitis; Fractional dose inactivated poliovirus vaccine; Routine immunization; Seroprevalence assay; Ecuador

Background

The World Health Organization (WHO) region of the Americas was certified poliovirus free in 1994 with the last indigenous case of poliomyelitis caused by wild poliovirus in 1991. Since then, it has been recognized that polio eradication is possible, and the region has maintained this status. The Americas is part of the global strategy to eradicate polio, which aims to eliminate the virus from the world by 2026. The Americas region has made significant progress toward this goal, with a reduction in reported cases of wild poliovirus from around the world. However, polio remains a global health threat, and continued vigilance and ongoing efforts are necessary to achieve the goal of polio eradication.
Research in context

Evidence before this study
Fractional dose (1/5th of full dose) of Inactivated Poliovirus Vaccine (fIPV) has demonstrated good immunogenicity and safety in clinical trials, however, limited data existed on immunogenicity of fIPV when used in national routine immunization programs.

Added value of this study
We compared immunogenicity of two doses of fIPV achieved in Ecuadorian routine immunization program and compared it with immunogenicity of full dose IPV schedule that had been used in Ecuador previously. We found that children who received 2 fIPV doses had higher titer of polio antibodies against serotype 2 poliovirus than those who received 1 full IPV dose; and similar titers against serotypes 1 and 3.

Implications of all the available evidence
Our data provide real-life evidence that fIPV is a beneficial and likely cost-effective option in polio immunization; and provides an example for other countries considering use of fIPV.

Poliovirus (WPV) detected in Peru in 1991. Globally, in 2021, there have been only 5 cases of poliomyelitis caused by WPV; four from Afghanistan and one from Pakistan - the last two remaining endemic countries. Nevertheless, in this period, many more paralytic cases of poliomyelitis were caused by vaccine-derived polioviruses (VDPVs), around 550 in 2021.

VDPVs result from use of live oral poliovirus vaccines (OPVs), which in rare circumstances regain neurovirulence following prolonged circulation in underimmunized populations. Outbreaks of circulating VDPV (cVDPV) continue to be detected in many African and Asian countries, with the vast majority being serotype 2 (cVDPV2). In the WHO region of Americas, an outbreak of cVDPV type 1 was detected in 2000-2001 on the island of Hispaniola; additionally, sporadic isolations of various VDPVs have been reported in different countries since then.

Because of the risk of VDPV, the Global Polio Eradication Initiative (GPEI) launched a strategy of phased withdrawal of vaccine poliovirus strains (referred to as Sabin stains) from OPV, starting with serotype 2. The first phase of this withdrawal was the switch from trivalent OPV (tOPV) containing all three poliovirus serotypes to bivalent OPV (bOPV) containing only serotypes 1 and 3. The switch was carried out in a globally synchronized manner in April 2016 and since then only bOPV in combination with inactivated poliovirus vaccine (IPV) has been used in routine immunization programs worldwide. Since 2016, IPV is the only vaccine used in routine immunization programs that provides protection against type 2 poliovirus.

Instead of a predicted decreasing trend of paralytic cases caused by cVDPV2 when tOPV was withdrawn in 2016, there has been an expansion in geographic scope and in numbers of cVDPV2 cases since the switch (71 in 2018; 366 in 2019; >1,100 in 2020, and 350 in the first 9 months of 2021). This situation poses risks to all countries in the world, including Ecuador, a country in the WHO region of the Americas. Although no cases or isolations of WPV or VDPVs have been reported in more than two decades, the country needs to maintain high level of serological protection among its population to mitigate outbreaks of paralytic poliomyelitis in case of an importation event of WPV or VDPV, especially VDPV2.

Ecuador uses both bOPV and IPV in its routine immunization schedule. One dose of IPV administered at 2 months of age was added to the immunization schedule in December 2015 in anticipation of the switch from tOPV to bOPV; and in line with the recommendation of the Strategic Advisory Group of Experts on Immunization (SAGE). Serotype 2 immunogenicity of one IPV dose varies with age of administration, with Poliovirus immunogenicity reaching about 50% when IPV is administered at 2 months of age. Aware of risk of VDPV2 importation, health officials sought ways to increase the immunity against serotype 2 in the polio immunization schedule. However, the cost of IPV and global IPV stock shortages between 2016 and 2019 were important barriers to the introduction of multiple IPV doses in Ecuador.

Intradermal administration of one-fifth of a full IPV dose (0.1 mL instead of 0.5 mL) referred to as fractional IPV or fIPV has been evaluated and recommended in a two-dose schedule by SAGE. This schedule provides superior immunogenicity compared to one full dose of IPV and stretches the existing supply of IPV while providing cost savings. Countries that introduced fIPV reported no major challenges with training and administration of intradermal vaccine. However, there was concern that intradermal injection is considered to be difficult and may result in poor immunogenicity of the vaccine if administered improperly.

Taking into consideration the SAGE recommendation, the existing clinical trial data on fIPV demonstrating good immunogenicity, no safety concerns, and the experience with fIPV use in other countries, Ecuadorian health authorities decided to replace one dose of full IPV with two doses of fIPV in the routine immunization schedule. This change occurred on January 1, 2018.
Since then, two doses of fIPV have been administered intradermally to all children at 2 and 4 months of age (replacing one full IPV dose that had been administered at 2 months of age). bOPV schedule was also changed on January 1, 2018 to 6, 18 month and 5 years (bOPV had been administered previously at 4, 6, and 18 months). The vaccination coverage assessed jointly by UNICEF and WHO has been ~ 80% with IPV or fIPV as well as with the last dose of bOPV for several years prior to 2020, decreasing to about 70% in the COVID-19 pandemic year of 2020. There was no significant difference between coverage with one IPV dose (prior to 2018) at 2 months of age and two fIPV doses at 2 and 4 months of age (after January 2018).25

We carried out a study comparing seroprevalence of poliovirus antibodies achieved by immunization schedules before and after the replacement of one dose of IPV with two doses of fIPV with the objective to describe the difference in achieved immunogenicity. The primarily focus was on poliovirus serotype 2 but we also report seroprevalence and antibody titres for serotypes 1 and 3.

**Methods**

This was a community-based, cross-sectional serological survey carried out between October 2020 and March 2021. Children with documented vaccination with either one dose of IPV or two doses of fIPV administered in 2017 or 2018, respectively, were eligible for enrolment.

Study sites (health centres) were selected from a list of functional state-run health centres in the three geographic regions of the country (Coastal, Andean, and Amazonia). Only health centres that vaccinated at least 50 children during a 3-month period were selected. Four centres were randomly selected in each of the geographic regions, in a way that two were located in the northern area and two in the southern area of each region (Table 1). Health officers in each selected health centre prepared a list of children that fulfilled inclusion criteria. These children were invited to participate and, if consented, were enrolled. The number of children invited in each health centre was proportionate to the size of population served by that health centre.

The study procedures were carried out during one health centre visit. After obtaining informed consent from parents, the children were enrolled. A simple demographic questionnaire including documented poliovirus vaccination history was administered and children’s Mid-Upper Arm Circumference (MUAC) was recorded. Children with MUAC <11.5 cm were not enrolled. Acute malnutrition was defined as MUAC between 11.5 and 12.5 cm. Approximately 2 mL of peripheral blood was drawn using aseptic technique by a trained phlebotomist. Extraction of sera was performed and the sera were shipped to the Centres for Disease Control and Prevention (CDC) in Atlanta, USA and tested for the presence of poliovirus neutralizing antibodies using standard microneutralization assay.26 Antibody titres for all three serotypes were reported in a log₂ scale. Seropositivity was defined as reciprocal titers of poliovirus neutralizing antibodies ≥8 (≥ 3 in log₂ scale). Highest reported antibody titer was 1:1,448 (10⁻⁵ in log₂ scale). In addition, haemoglobin quantification was performed at the time of blood draw using HemoCue (Angelholm, Sweden), a point of care test. Low haemoglobin indicating possible anaemia was defined as a concentration of less than 11.0 g/dL with correction made for altitude.28 Attribution of health centres to urban/peri-urban/rural was established based on classification of Ecuadorian Ministry of Health.

The required sample size to show that the difference between the seroprevalence of serotype 2 antibodies is at least 10% (between the children who received two doses of fIPV versus those who received one full IPV dose) at an estimated seroconversion after 2 fIPV doses of 70% was found to be 117 in each group. Accounting for an attrition of 10% and design effect of 1.5, the minimum sample size required was 296; we rounded this up to 300 or 150 in each group.

Seroprevalence against all three poliovirus serotypes was expressed as percentages with 95% confidence intervals. Seroprevalence was compared between the groups who received IPV or fIPV using Chi-square test. Variables associated with type 2 seropositivity were identified using Chi-square test and logistic regression. A p value < 0.05 was considered significant. The distribution of titres was presented using median and reverse cumulative curves for all three serotypes. The analysis of data was carried out using R software version 3.6.0.29

**Table 1: Geographic distribution of study sites in Ecuador.**

| Region  | Study Site                   |
|---------|------------------------------|
| Amazonia| Archidona                    |
|         | Joya de los Sachas           |
|         | Morete Puyo                  |
|         | Urbano Puyo                  |
|         | Guayaquil Bastion Popular    |
|         | Guayaquil No 11              |
|         | Montecristi                  |
| Sierra  | Santo Domingo                |
|         | Catacocha                    |
|         | Cuenca                       |
|         | El Quinche                   |
|         | Otavalo                      |

**Ethical approval**

The protocol was reviewed and approved by the Human Research Ethics Committee - CEISH-USFQ and by the Ethics Review Committee at the WHO in Geneva.
Role of the funding source
WHO obtained funds for the study from Rotary International. The funders had no role in study design, data collection, data analysis, interpretation, or writing of the report.

Results
There were 358 children invited to participate in the study and 329/358 (91.9%) were enrolled. The remaining 29 children either did not meet inclusion criteria or their parents did not provide consent to participate in the study. We included 321/329 (97.6%) of enrolled children in the analysis; the remaining 8 children did not provide analysable samples of blood. In our final sample of 321 participants, there were 160 (49.8%) children who had documented vaccination with one full IPV dose and 161 (50.2%) children with documented vaccination with two fractional IPV doses.

Children who received IPV were similar to those who received fIPV in gender, place of residence, and haemoglobin levels. However, the two groups were significantly different in age (median age 39 vs 35 months for IPV and fIPV groups respectively, p<0.001), in the time interval between the administration of the last IPV dose and blood collection (median interval 37 vs 30 months for IPV and fIPV groups respectively, p<0.001), vaccination history with bOPV, and MUAC (Table 2). In our sample, there were no children with acute malnutrition.

Seroprevalence of serotype 1 poliovirus neutralizing antibodies was 100% (CI95%=97.0-100%) and 99.4% (CI95%=96.5-99.9%) for IPV and fIPV groups respectively; 50.0% (CI95%=44.2-55.8%) and 83.2% (CI95%=78.5-87.1%) for serotype 2; and 97.5% (CI95%=92.2-99.2%) and 92.5% (CI95%=83.9-96.7%) for serotype 3 (Figure 1). For serotype 2, the difference between IPV and fIPV groups was significant (p<0.001); for serotypes 1 and 3 there was no statistically significant difference between these groups (p=1.00 for serotype 1; and p=0.07 for serotype 3).

Median antibody titers did not differ between IPV and fIPV groups for serotypes 1 and 3 (for serotype 1 it was 10-5; and for type 3 it was 9-5 for both IPV and fIPV groups); serotype 2 antibody titers were significantly lower for the IPV group than for fIPV recipients (3.0, CI95%=3.3-5.9 vs. 4.8, CI95%=4.5-5.2, p<0.001). Reverse cumulative distribution curves for types 1, 2, and 3 are presented in Figure 2 (panels A, B, and C).

We performed univariate analysis of risk factors associated with serotype 2 seroprevalence in each group separately. In either group, the seroprevalence of serotype 2 antibodies did not significantly differ with either gender, or age, or any other risk factors (Table 3). Low hemoglobin showed borderline association with lower seropositivity for serotype 2 in fIPV group. We performed multivariate analysis separately for IPV and fIPV groups; in the model we included gender, age, residence, and Hb level; and found no significant risk factors (Supplementary Table 1).

Discussion
Our study provides evidence that two doses of fIPV (administered intradermally at 2 and 4 months of age in the routine immunization program in Ecuador) resulted in significantly higher seroprevalence and antibody titres against poliovirus serotype 2 than one dose of IPV (administered at 2 months of age). The health officials in Ecuador made correct decision to replace one full IPV dose with two fIPV doses: better protection against polio was achieved while saving vaccine supply and cost. We have not identified any risk factors associated with seronegativity for serotype 2 including geographic regions of Ecuador or age.

The serotype 2 immunogenicity achieved in our study with two doses of fIPV was similar to previous clinical trial results.30–34 This finding provides evidence

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Table 2: Demographic indicators, vaccination history, mid-upper arm circumference, and haemoglobin levels by vaccinated group (fIPV vs. IPV), Ecuador.
that fIPv was administered successfully via intradermal route in routine immunization and that initial vaccination training was effective.

Seroprevalence and antibody titres against poliovirus serotypes 1 and 3 were, as expected, high. This is a result of multiple doses of bOPV in combination with IPV or fIPv received as part of the routine immunization program and provides evidence that the EPI program in Ecuador is functional when it reaches children.

To our knowledge, this is the first study where blood samples were collected about 3 years after the last IPV dose was administered in the absence of known exposure to serotype 2 poliovirus during this period. We expected to see waning of antibody titres during this period as described in previous clinical trials. However, we cannot assess to what extent waning occurred as we do not have blood samples from earlier time points for comparison. Antibody titres in our study were similar to those reported in clinical trials in which samples had been collected one month after the last IPV dose. We hypothesise that the selected Ecuadorian paediatric population may be healthier than their peers in less developed countries where clinical trials had been conducted, resulting in a more robust and longer lasting immune response to vaccination. However, we do not have sufficient data in this study for a conclusive answer.

Our study had some limitations. The COVID-19 pandemic seriously affected study timelines and implementation – the study was planned to be carried out in early 2020, however, pandemic restrictions resulted in more than a year delay. In addition, the health centre classification (urban/rural) may not necessarily correspond to the type of population served.

SAGE currently recommends at least two IPV doses (full or fractional) in routine immunization schedules for all countries. SAGE suggested that there should be at least 4 months of interval between doses. Now that IPV supplies have stabilized, Ecuador will face a decision to either maintain the current routine immunization schedule or to make changes. The preferred option would be to extend the interval between fIPv doses to the recommended 4 months in order to optimize type 2 immunogenicity. Changing back to a two-dose full IPV schedule is another option, albeit the small gain in immunogenicity may not justify the significant increase in cost.

Although poliovirus has been certified eradicated in the American region, all countries need to maintain high population immunity against polio and strengthen their outbreak response capacity in order to mitigate the spread of paralytic disease in case of poliovirus importation. Further cost-effectiveness and cost-containment analysis will provide definitive answers to whether schedules including fIPv provide a cost-effective option, while our report confirms it provides robust protection against paralytic outbreaks of polioviruses.

Figure 1. Seroprevalence of type-specific poliovirus neutralizing antibodies for individuals receiving fractional inactivated poliovirus vaccine (fIPv) or inactivated poliovirus vaccine (IPV) [95% confidence interval shown by error bars].
Figure 2. Reverse cumulative distribution curves of antibody titers for types 1, 2, and 3 for individuals receiving fIPV (gray line) or IPV (dark line) [titers on x axis expressed in log₂ scale].
**Contributors**

GT VJ OM: protocol preparation, data collection, data verification, data analysis, manuscript preparation; BM YZ: laboratory analysis, manuscript preparation; LL AW AO GB RR JZ GS DM EQ ACH GR: data verification, data analysis, manuscript preparation.

**Disclaimer**

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the contributing agencies.

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**Data sharing statement**

Identifiable data will not be shared. Anonymised data and protocol may be shared at publication upon request to the corresponding author, Dr. Ondrej Mach.

**Declaration of interests**

None declared, all authors.

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**Supplementary materials**

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2022.100235.

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| Risk factors | IPV Group Type 2 (Positivity) | RIVP Group Type 2 (Positivity) |
|-------------|-------------------------------|-------------------------------|
|             | n/N  | %   | p value | n/N | % | p value |
| Female child| 35/81| 43.2% | 0.114 | 68/79 | 86.1% | 0.461 |
| Male child  | 45/79| 57.0% | 66/82 | 80.5% |
| Age         |      |      |        |      |      |
| <2.5 years  | 0    |      |        | 21/24 | 87.5% | 0.92* |
| 2.5–<3 years| 0    |      |        | 67/81 | 82.7% |
| 3–<3.5 years| 61/127| 48.0% | 0.54*| 46/56 | 82.1% |
| 3.5–<4 years| 15/27| 55.6% | 0    | 0    |
| >=4 years   | 4/6  | 66.7% | 0    | 0    |
| Hb <11 g/dl | 2/9  | 22.2% | 0.167| 15/22 | 68.2% | 0.058 |
| Hb>11 g/dl  | 78/151| 51.7% |    | 119/139 | 85.6% |
| Rural area  | 17/32| 53.1% | Ref. | 34/41 | 82.9% | Ref. |
| Peri-urban  | 8/17 | 47.1% | 0.677| 15/18 | 83.3% | 0.998 |
| Urban       | 55/111| 49.5% | 0.908| 85/102 | 83.3% | 0.998 |
| Region of Ecuador |   |      |      | 42/50 | 84.0% | Ref. |
| Sierra      | 20/50| 40.0% | Ref. | 51/61 | 83.6% | 0.219 |
| Costa       | 40/72| 55.6% | 0.091| 41/50 | 82.0% | 0.97 |
| Amazonia    | 20/38| 52.6% | 0.246|      |      |      |

Table 3: Analysis of risk factors associated with type 2 seropositivity (univariate analysis).

* p value represents difference across all age-group strata.
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