X Ad Hoc Meeting of the PAHO Technical Advisory Group (TAG) on Vaccine-Preventable Diseases

31 May 2023
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# Abbreviations and Acronyms

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>aP</td>
<td>acellular pertussis</td>
</tr>
<tr>
<td>AFP</td>
<td>acute flaccid paralysis</td>
</tr>
<tr>
<td>bOPV</td>
<td>bivalent oral polio vaccine</td>
</tr>
<tr>
<td>cVDPV</td>
<td>global circulating vaccine-derived poliovirus (Also with 1, 2, or 3 for type, e.g., cVDPV1, cVDPV2, cVDPV3)</td>
</tr>
<tr>
<td>DTP</td>
<td>diphtheria tetanus toxoid and pertussis (Also, DTP3: Diphtheria Tetanus toxoid and Pertussis third dose)</td>
</tr>
<tr>
<td>DTwP</td>
<td>diphtheria, tetanus, whole-cell pertussis</td>
</tr>
<tr>
<td>EPI</td>
<td>expanded program on immunization</td>
</tr>
<tr>
<td>ESAVI</td>
<td>events supposedly attributed to vaccination or immunization</td>
</tr>
<tr>
<td>fIPV</td>
<td>fractional dose inactivated polio vaccine</td>
</tr>
<tr>
<td>Gavi</td>
<td>The Vaccine Alliance</td>
</tr>
<tr>
<td>HepB</td>
<td>hepatitis B</td>
</tr>
<tr>
<td>Hib</td>
<td>haemophilus influenzae type b</td>
</tr>
<tr>
<td>HPV</td>
<td>human papillomavirus</td>
</tr>
<tr>
<td>IHR</td>
<td>International Health Regulations</td>
</tr>
<tr>
<td>IRR</td>
<td>incidence rate ratio</td>
</tr>
<tr>
<td>IPV</td>
<td>inactivated polio vaccine</td>
</tr>
<tr>
<td>mOPV2</td>
<td>monovalent oral polio vaccine type 2</td>
</tr>
<tr>
<td>nOPV2</td>
<td>novel oral polio vaccine type 2</td>
</tr>
<tr>
<td>OPV</td>
<td>oral polio vaccine</td>
</tr>
<tr>
<td>PAHO</td>
<td>Pan American Health Organization</td>
</tr>
<tr>
<td>PHEIC</td>
<td>public health emergency of international concern</td>
</tr>
<tr>
<td>PIRI</td>
<td>periodic intensification of routine immunization</td>
</tr>
<tr>
<td>PR</td>
<td>prevalence ratio</td>
</tr>
<tr>
<td>PV1</td>
<td>poliovirus type 1</td>
</tr>
<tr>
<td>PV2</td>
<td>poliovirus type 2</td>
</tr>
<tr>
<td>RCC</td>
<td>Regional Certification Commission for the Polio Endgame in the Region of the Americas</td>
</tr>
<tr>
<td>RI</td>
<td>routine immunization</td>
</tr>
<tr>
<td>RSV</td>
<td>Respiratory Syncytial Virus</td>
</tr>
<tr>
<td>SAGE</td>
<td>Strategic Advisory Group of Experts</td>
</tr>
<tr>
<td>tOPV</td>
<td>trivalent oral polio vaccine</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations International Children's Emergency Fund</td>
</tr>
<tr>
<td>VPD</td>
<td>vaccine preventable disease</td>
</tr>
<tr>
<td>VDPV1</td>
<td>Vaccine-derived poliovirus type 1 (Also, with 2 or 3 for alternate types, e.g., VDPV2, VDPV3)</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WPV1</td>
<td>wild poliovirus type 1</td>
</tr>
<tr>
<td>wP</td>
<td>whole-cell pertussis</td>
</tr>
<tr>
<td>WUENIC</td>
<td>WHO/UNICEF Estimates of National Immunization Coverage</td>
</tr>
</tbody>
</table>
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*Not present during the meeting.
Background

In July 2021, the Technical Advisory Group (TAG) on Immunizations for the Americas stated, "The Region is facing an impending crisis around routine vaccination." At that time, 1.7 million children younger than one year in the Americas (14%) had never received a single dose of vaccine. Brazil and Mexico reported about half of this figure.

Across the Region, 2.7 million children in the same age cohort – nearly one in five – were under-vaccinated. One year later, in July 2022, the United States reported its first case of vaccine-derived poliovirus type 2 (VDPV2) since 2013. One month later, Canada reported positive wastewater samples for circulating VDPV2. In March 2023, Peru reported one confirmed case of VDPV1—a zero-dose child with no history of travel in the province of Loreto, on the border with Brazil and Colombia.

During its last meeting, the TAG recommended countries and territories focus their political, technical, and financial commitment to halt the decline in vaccination coverage by December 2023. Given the risk of importation and emergence of global circulating vaccine-derived poliovirus (cVDPV), countries that have not yet introduced the second dose of inactivated polio vaccine (IPV) should do so immediately to reduce the pool of children susceptible to poliovirus type 2 (PV2).

During the 31 May 2023 meeting, the PAHO secretariat presented to TAG members an update on the polio situation in the Americas. The secretariat proposed the co-administration of oral polio vaccine (OPV) and inactivated polio vaccine (IPV) in response to polio events or outbreaks to continue closing immunity gaps as quickly and effectively as possible and to bolster immunity in hard-to-reach populations.

Additionally, the secretariat provided the latest information on whole-cell pertussis (wP) hexavalent vaccine and asked TAG members to provide considerations for the PAHO Director, Dr. Jarbas Barbosa, to guide countries and territories that are evaluating its introduction in the national immunization schedule.

Finally, the TAG recommended the use a one-dose HPV vaccination schedule for all girls 9 through 14 years of age if immunogenicity of the vaccine product and long-lasting immunity conferred by the one-dose schedule have been documented.
Current polio situation in the Americas and the use of polio vaccines to respond to an event or outbreak

Question for the TAG

- Should the Region’s countries consider the simultaneous administration of bivalent oral polio vaccine (bOPV) and IPV in response to polio events or outbreaks and hard-to-reach populations?

The Use of Polio Vaccines in Hard-to-Reach Populations and Responding to Polio Events or Outbreaks

Polio epidemiological update

In May 2014, the World Health Organization (WHO) Director-General declared the international spread of poliovirus a Public Health Emergency of International Concern (PHEIC) under the International Health Regulations (IHR).

Ever since, as requested, the Emergency Committee has reassessed the situation every three months (1). The thirty-fifth meeting of the Committee took place on 3 May 2023. After reviewing the data on wild poliovirus type 1 (WPV1) and circulating derived polioviruses (cVDPV), the Committee concluded that the international spread of polio continues to be a PHEIC (2).

Only two countries (Afghanistan and Pakistan) remain endemic for WPV1. However, in 2022, one case in Malawi and eight cases in Mozambique were reported as part of an outbreak that started with an imported case in Malawi. cVDPV cases continue to be an essential obstacle toward polio eradication. In 2022, 186 cases of cVDPV1 were reported (145 in the Democratic Republic of the Congo, 14 in Madagascar, 22 in Mozambique, four in Malawi, and one in Yemen). Twenty countries reported 675 cVDPV2 cases, and Israel reported one cVDPV3 case.

In the Region of the Americas, there is an increasing risk of having a polio outbreak after the importation of WPV1, cVDPV, or the emergence of a VDPV1 or VDPV3 in the Region. Many countries continue with low immunization coverage and underperforming surveillance systems. The preliminary regional immunization coverage for 2022, with data from 29 member states and five territories for polio3, is 83% (3).

However, there is heterogeneity in the national coverage reported by countries and significant gaps at the municipal level. Only ten countries in the Region reported polio3 coverage >95%, while nine reported a coverage <80%. The regional acute flaccid paralysis (AFP) rate was 1.32 in 2022. Health staff investigated 92% of the cases within 48 hours after notification, and 77% had an adequate sample (4, 5).

A case of paralytic polio caused by cVDPV2 was detected in an unimmunized, immunocompetent young adult with no history of travel during the exposure period in Rockland County, New York, USA, with onset of paralysis on 20 June 2022 (6).
A retrospective analysis of wastewater samples confirmed ongoing circulation since April 2022 of genetically linked polioviruses to the case. Health staff collected the last cVDPV2-positive wastewater samples in October 2022 in Rockland County, New York, USA. Health staff have genetically linked the cVDPV2 from the USA to the viruses isolated in wastewater samples in Israel and the United Kingdom.

Through the retrospective analysis of wastewater samples in Canada in areas with close relations with the affected community in the USA, health staff detected two cVDPV2 cases genetically linked with the polio case in New York in wastewater samples collected in August 2022 from two different collection sites (7, 8). One of the samples was collected from a wastewater treatment plant (with eight nucleotide changes), and one from an environmental sampling site (with six nucleotide changes).

All subsequent samples collected in Canada (n=23) were negative for poliovirus, including specimens collected between 31 October and 9 November 2023. Until 24 May 2023, health staff reported no other polio cases linked with this poliovirus in the Region of the Americas.

Officials detected a case of paralytic polio caused by a VDPV1 in an unimmunized, immunocompetent, 14-month-old child with no history of travel who belongs to an indigenous community in the district of Manseriche in the Datem del Maranon province of the Loreto department in Peru (9). The genetic sequence has 31 nucleotide differences in the Sabin 1 PV1 region and is not genetically related to any previously sequenced VDPV1s. The investigation and public health response are still ongoing.

**Background information**

Oral polio vaccine (OPV) excretes in stools and spreads from person to person, increasing the protection in the community. However, in communities with low vaccination rates, the virus can circulate for an extended time and can rarely mutate to vaccine-derived polioviruses (VDPV) that can cause paralysis (10). For this reason, to eradicate polio, the cessation of OPV use will be necessary after poliovirus transmission is stopped (11).

Health providers eradicated WPV2 in 1999, and therefore, the type 2 serotype component in trivalent OPV caused all the cases of type 2 paralytic polio, and over 90% of cVDPV cases were type 2 (11). Therefore, in April 2016, in a coordinated manner, health officials replaced the trivalent OPV vaccine with the bivalent OPV (bOPV) version, which contains only serotypes 1 and 3 (11).

As stated by Macklin et al., "the number and geographic breadth of cVDPV2 outbreaks detected after the withdrawal of type 2 containing OPV have exceeded forecasts" (12). Officials associate the reported outbreaks after the switch with low immunization and population immunity that could be related to the higher prevalence of factors that interfere with the vaccine, making it less immunogenic, including malnutrition, diarrhea, or infection by other enteroviruses (12, 13).

A monovalent OPV vaccine containing only serotype 2 (mOPV2) is available for outbreak response in an emergency stockpile that WHO and UNICEF manage. However, many vaccination
campaigns implemented in response to the cVDPV2 outbreaks have been suboptimal, resulting in further virus seeding (12). A paper published by Macklin et al. indicates the timeline of cVDPV2 emergences between 2016 and 2020, and the probability of seeding before or after the switch (14).

Pharmacologists developed a new vaccine, the novel oral polio vaccine type 2 (nOPV2), to stop further spread, which is more genetically stable for outbreak response (15). Even though all the evidence has demonstrated that the novel vaccine has a significantly lower risk of reverting to a form that causes paralysis in low immunity settings when compared to mOPV2, in March 2023, health officials detected cVDPV2 linked with the nOPV2 in Burundi and the Democratic Republic of the Congo (16).

OPV has an inferior immunogenicity in tropical countries. A possible solution is an OPV-containing vaccine and IPV administered simultaneously. Studies conducted in several countries have shown that combined inactivated poliovirus vaccine (IPV) and OPV schedules induce a favorable immunological response and appear to correct for the lower immunogenicity of OPV in developing countries (17).

Data from a study conducted in 51 countries in Africa showed that "immunity from IPV has a significant effect on reducing the incidence of cVDPV2 cases, with a 1.3-fold decrease in incidence per 10% absolute increase in population immunity (adjusted incidence rate ratio 0.79, 95% credible interval [CrI] 0.64-0.95) (18).

In Nigeria, campaigns with IPV and trivalent OPV (tOPV) substantially reduced the incidence of poliomyelitis caused by cVDPV2. The incidence rate ratio (IRR) was 0.17 for 90 days after vs. 90 days before campaigns, 95% confidence interval [CI] 0.04–0.78. The virus's prevalence ratio (PR) in environmental samples was 0.16, 95% CI 0.02–1.33.

In Pakistan, results suggest that administering IPV alongside OPV can decrease poliovirus transmission if high vaccine coverage is achieved (19). The authors updated the estimates in Pakistan, including an extended surveillance period and additional campaigns when wild-type 1 poliovirus has been circulating. Results from Pakistan showed that adding IPV to OPV improved the immunological response and shortened the duration of poliovirus shedding (20).

A review of IPV use in campaigns to control cVDPV2 outbreaks shows that "provision of supplementary doses of IPV in combination with OPV in campaigns in populations with difficult access for routine immunization (RI) or high risk of OPV failure could, in theory, close humoral immunity gaps and boost mucosal immunity to poliovirus with fewer vaccination encounters, thus accelerating interruption of transmission in outbreaks" (13).

In March 2023, the Strategic Advisory Group of Experts (SAGE) recommended that in areas of persistent poliovirus circulation, health practitioners conduct an additional IPV campaign to supplement nOPV2 and Sabin OPV campaigns as a means to enhance mucosal immunity and reduce the likelihood of ongoing poliovirus circulation (21).

The TAG has not previously discussed the co-administration of IPV and an OPV-containing vaccine for outbreak response and in hard-to-reach populations. However, the TAG recommended in 2022 that in locations where polio3 coverage rates fall below 80%, countries strengthen routine immunization service delivery and implement multi-antigen catch-up vaccination operations—periodic intensification of routine immunization (PIRI) activities, innovative local strategies (e.g.,
mobile vaccination teams, outreach activities, events where health personnel offer multiple health services to the public in one location)—to close the immunity gap (22).

Some countries in the Region of the Americas and other Regions have conducted campaigns using IPV and OPV. One campaign evaluation in Kenya demonstrated that the co-administration of these vaccines is feasible; Kenya achieved a high coverage rate (>90%). However, these campaigns come at a higher cost and require greater attention to vaccinator training and supervision (23).

The review of the use of IPV in campaigns to control cVDPV2 outbreaks as of March 2021 in 78 campaigns delivering IPV (n=73) or fractional dose IPV (fIPV) (n=5) as part of the response to WPV1 or cVDPV2 circulation demonstrated the operational feasibility of IPV campaigns (13).
Introduction of the wP hexavalent vaccine in countries/territories of the Americas

**Question for the TAG:**
- What should countries and PAHO consider for the introduction of wP hexavalent in the routine immunization schedule once available?

**Background information**

Information on the inactivated polio vaccine and the third dose of diphtheria, tetanus toxoid, and pertussis (DTP3) containing vaccines in countries/territories of the Americas

**Figure 1. Coverage – DTP-containing vaccine, 3rd dose – Administrative coverage by country – 2022.**

Before the COVID-19 pandemic, DTP coverages had fallen from 95% in 2017 to 92% in 2018 for the first dose and remained at 88% for the third dose of the vaccine. DTP vaccination rates have continued to fall with the pandemic—disrupting regional health services, including routine immunization. In 2022, only 80% of children received the third dose of DTP in the Region (Figure 1 and Table 1) (24).
Table 1. Diphtheria tetanus toxoid and pertussis (first and third dose) vaccination coverage, Region of the Americas.

<table>
<thead>
<tr>
<th>Region of the Americas</th>
<th>Antigen</th>
<th>Data source</th>
<th>2022</th>
<th>2021</th>
<th>2020</th>
<th>2019</th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTP-containing vaccine, first dose</td>
<td>WUENIC</td>
<td>86%</td>
<td>88%</td>
<td>89%</td>
<td>92%</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DTP-containing vaccine, third dose</td>
<td>WUENIC</td>
<td>80%</td>
<td>81%</td>
<td>84%</td>
<td>88%</td>
<td>88%</td>
<td></td>
</tr>
</tbody>
</table>


Globally, only 45 countries (23%) have only one dose of IPV in their immunization schedule. In the American Region, only Haiti has yet to introduce a second dose of IPV (Figure 2).

Figure 2. IPV schedules in routine immunization globally.

Whole-cell (wP) and acellular (aP) pertussis vaccines.

Despite effective infant immunization programs and high vaccination coverage in developed countries, pertussis has re-emerged worldwide in non or partially-vaccinated infants, adolescents, and adults. The switch from whole-cell pertussis (wP) to acellular pertussis (aP) vaccines in some countries did not cease pertussis re-emergence but rather contributed to the increased incidence of pertussis (25).

New evidence suggests that the immunity conferred by the aP vaccine has a shorter-lived duration of protection than wP vaccines (25). Therefore, since 2012, the TAG advised countries not to
switch from wP pertussis to aP vaccines for the primary infant vaccination series and to initiate vaccination schedules at six weeks of age in outbreak situations (26).

The wP hexavalent (DTwP-Hib-HepB-IPV)\(^1\) vaccine

Considering the pre and post-polio eradication contexts, currently available licensed product, supply pipeline, timeline of IPV-containing wP hexavalent, and Gavi’s planning effort, SAGE held a meeting in October 2021 to discuss and provide recommendations on supporting the wP hexavalent vaccine.

Pending WHO prequalification, SAGE agreed in principle to administer a wP hexavalent vaccine using the early schedules currently recommended for the pentavalent vaccine co-administered with IPV (i.e., at two, three, and four months or six, ten, and 14 weeks plus a fourth dose booster). A primary three-dose hexavalent schedule starts from six weeks of age, with a minimum interval of four weeks (27, 22).

Studies reviewed demonstrated a good safety and immunogenicity profile of the wP hexavalent vaccine for infant primary series vaccination at six to eight, ten to twelve, and 14 to 16 weeks, with booster vaccination at 15–18 months of age (28). The immunogenicity and safety profiles of wP vaccines are non-inferior to the commercially available Penta and IPV vaccines (29, 30) (Table 2). Hitt Sharma et al. stated that no immediate adverse events were observed within 30 minutes of vaccination. The authors reported 67 solicited adverse events and five unsolicited. Pain at the injection site (70.8%), irritability (75%), and fever (58.3%) were the most reported solicited adverse events (Table 3).

The wP hexavalent vaccine market potential dynamics and pricing benchmarks

Currently, there are few providers in the process of WHO prequalification. Officials project that by the end of 2023, WHO will prequalify one of these products. Moreover, stakeholders expect that the hexavalent market will evolve from a dominant supplier period in 2023 – 2026 to a more competitive period starting in 2027. Table 4 provides details on wP hexavalent providers.

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\(^1\) DTwP = Diphtheria, Tetanus, whole-cell Pertussis; Hib = *Haemophilus influenzae* type b; HepB = Hepatitis B; IPV = Inactivated Polio Vaccine.
Table 2. Summary of adverse events reported during the clinical trial of the EasySix™ vaccine.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>EasySix™ (N = 142)</th>
<th>Pentavac SD™ co-administered with Inovac Polio™ (N = 142)</th>
<th>Total subjects in vaccinated cohort (N = 284)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AEs reported</td>
<td>100 (70.42)</td>
<td>106 (74.64)</td>
<td>206 (72.53)</td>
</tr>
<tr>
<td>Unsolicited AEs</td>
<td>1 (0.70)</td>
<td>2 (1.40)</td>
<td>3 (1.05)</td>
</tr>
<tr>
<td>Solicited AEs</td>
<td>99 (69.71)</td>
<td>104 (73.23)</td>
<td>203 (71.47)</td>
</tr>
<tr>
<td>Solicited local AEs</td>
<td>79 (55.63)</td>
<td>84 (59.15)</td>
<td>163 (57.39)</td>
</tr>
<tr>
<td>Pain/Tenderness</td>
<td>72 (50.70)</td>
<td>74 (52.11)</td>
<td>146 (51.40)</td>
</tr>
<tr>
<td>Redness</td>
<td>27 (19.01)</td>
<td>13 (9.15)</td>
<td>40 (14.00)</td>
</tr>
<tr>
<td>Swelling</td>
<td>35 (24.64)</td>
<td>22 (15.49)</td>
<td>57 (20.07)</td>
</tr>
<tr>
<td>Solicited systemic AE</td>
<td>81 (57.04)</td>
<td>74 (52.11)</td>
<td>155 (54.57)</td>
</tr>
<tr>
<td>Fever</td>
<td>81 (57.04)</td>
<td>74 (52.11)</td>
<td>155 (54.57)</td>
</tr>
<tr>
<td>Acute allergic reaction</td>
<td>1 (0.70)</td>
<td>0 (0)</td>
<td>1 (0.35)</td>
</tr>
<tr>
<td>Sleepiness/drowsiness</td>
<td>1 (0.70)</td>
<td>2 (1.4)</td>
<td>3 (1.05)</td>
</tr>
<tr>
<td>Irritability/restlessness/fussiness</td>
<td>11 (7.74)</td>
<td>11 (7.74)</td>
<td>22 (7.74)</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>0 (0)</td>
<td>2 (1.4)</td>
<td>2 (0.70)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (1.4)</td>
<td>1 (0.70)</td>
<td>3 (1.05)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0)</td>
<td>1 (0.70)</td>
<td>1 (0.35)</td>
</tr>
<tr>
<td>Any SAE reported</td>
<td>1 (0.70)</td>
<td>0 (0)</td>
<td>1 (0.35)</td>
</tr>
</tbody>
</table>

* Safety assessment data represented as number (n) and % (in parentheses) of subjects reporting adverse events (AEs) during the entire study.

Panacea Biotec Ltd manufactures the EasySix™ vaccine. All adverse events were entirely resolved without any sequelae. There were no fatalities reported.

Table 3. Post-vaccination incidence of solicited adverse events.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>e</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site pain</td>
<td>17</td>
<td>17</td>
<td>70.83</td>
<td>[48.91, 87.38]</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2</td>
<td>2</td>
<td>8.3</td>
<td>[1.03, 27.00]</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>4</td>
<td>4</td>
<td>16.7</td>
<td>[4.74, 37.38]</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NE</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>6</td>
<td>6</td>
<td>25</td>
<td>[9.77, 46.71]</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NE</td>
</tr>
<tr>
<td>Fever</td>
<td>14</td>
<td>14</td>
<td>58.3</td>
<td>[36.64, 77.89]</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NE</td>
</tr>
<tr>
<td>Irritability</td>
<td>18</td>
<td>18</td>
<td>75.0</td>
<td>[53.29, 90.23]</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NE</td>
</tr>
<tr>
<td>Abnormal Crying</td>
<td>2</td>
<td>2</td>
<td>8.3</td>
<td>[1.03, 27.00]</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NE</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5</td>
<td>5</td>
<td>20.8</td>
<td>[7.13, 42.15]</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1</td>
<td>1</td>
<td>4.2</td>
<td>[0.11, 21.12]</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>1</td>
<td>1</td>
<td>4.2</td>
<td>[0.11, 21.12]</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NE</td>
</tr>
</tbody>
</table>

e = Number of events, n = Number of subjects with adverse events, NE = Non Estimable, % = Percentages of subjects, CI = Confidence interval.

There were no immediate adverse events observed within 30 minutes of vaccination. None of the unsolicited events were related to the vaccination. No adverse events led to any discontinuation. The study reported no death or other serious adverse events.
Table 4. wP hexavalent vaccine providers.

<table>
<thead>
<tr>
<th>Supplier</th>
<th>Origin</th>
<th>Presentation</th>
<th>Situation</th>
</tr>
</thead>
</table>
| Serum Institute of India (ISI)| India  | • 1-dose vial  
• 10-dose vial  | It obtained marketing authorization in India in October 2022. WHO prequalification is expected around the third quarter of 2023. |
| Panacea                      | India  | • 1-dose vial  
• 4-dose vial  
• Prefilled syringe | Available in the Indian private market since 2017. WHO prequalification is planned for mid-2024. |
| Biological E. Limited*        | India  |                               | WHO prequalification is expected in the second quarter of 2026.           |
| LG Chem                      | South Korea |                               | In clinical trial phase. WHO prequalification could be possible around 2027. |

Six countries (Canada, USA, Mexico, Panama, Chile, and The Bahamas) in the Region already use the aP hexavalent vaccine (not wP hexavalent) as part of their routine schedule. Two countries (Barbados and Argentina) currently use the vaccine for high-risk populations (e.g., children of HIV-positive mothers in Barbados and premature babies in Argentina). Argentina plans to extend the aP hexavalent vaccine to its general population, and discussions are ongoing. Paraguay and El Salvador will introduce the aP hexavalent vaccine in 2023 (Figure 3).

**Figure 3. aP hexavalent vaccine – Region of the Americas, 2023.**

Considerations

• Currently, no WHO-prequalified wP hexavalent vaccines exist, so the Revolving Fund is not procuring this product. However, there is a plan to issue a tender on the condition of future prequalified products.

• The incorporation of the wP Hexavalent vaccine into national vaccination schedules will provide several advantages from a public health perspective:
  
  o By combining Pentavalent (primary series and a booster in the second year of life) and IPV, the hexavalent provides the same health impact as these two vaccines regarding cases and deaths averted.
  
  o As per previous TAG recommendations, "although both available pertussis vaccines (aP and wP) elicit a good immune response, evidence suggests aP has a short-lived duration of protection. Thus, countries should give preference to the use of wP containing vaccines" (31, 32).
  
  o The wP hexavalent vaccine would reduce the number of vials and injections, resulting in saved acquisition costs (syringes and safety boxes) and in-country expenses (e.g., cold chain, transportation, and labor).
  
  o Reducing fear of injections in children and parents.
  
  o Reduction of pain and discomfort after injections.
  
  o Reduction in the number of visits.

• The wP hexavalent vaccine provides an excellent safety and immunogenicity profile.

• Replacing pentavalent and standalone IPV with IPV containing wP hexavalent when products become available can be a smooth transition without major schedule adaptations.

• Countries should continue using bOPV to maintain mucosal immunity to poliovirus.

• Countries should consider previous TAG recommendations on pertussis, diphtheria, tetanus, and polio vaccines for their national vaccination schedule (Tables 5 and 6).
Table 5. Regional recommendation for polio vaccination schedule, Region of the Americas, 2021.

<table>
<thead>
<tr>
<th>Vaccination Schedule</th>
<th>Basic</th>
<th>1$^{st}$</th>
<th>2$^{nd}$</th>
<th>3$^{rd}$</th>
<th>4$^{th}$</th>
<th>5$^{th}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months</td>
<td>IPV</td>
<td>bOPV</td>
<td>IPV</td>
<td>bOPV</td>
<td>bOPV</td>
<td></td>
</tr>
</tbody>
</table>

The TAG recommended the above vaccination schedule for the 13 countries that have not yet introduced the second dose of IPV. TAG reiterates its previous recommendation that Member States not discontinue bOPV in favor of an IPV-only schedule in July 2022.

Table 6. Schedule for countries wishing to introduce wP hexavalent.

<table>
<thead>
<tr>
<th>Vaccination Schedule</th>
<th>Basic</th>
<th>1$^{st}$</th>
<th>2$^{nd}$</th>
<th>3$^{rd}$</th>
<th>4$^{th}$</th>
<th>5$^{th}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months</td>
<td>wP Hexavalent</td>
<td>wP Hexavalent + bOPV</td>
<td>wP Hexavalent</td>
<td>wP Hexavalent + bOPV</td>
<td>bOPV</td>
<td></td>
</tr>
</tbody>
</table>

Human papillomavirus (HPV) vaccination schedule in the context of cervical cancer elimination

**Question for the TAG**

- Should countries consider using the single-dose HPV schedule with any prequalified vaccine available in the market in the context of cervical cancer elimination?

**The burden of cervical cancer**

Cancer of the cervix uteri is the fourth most common cancer among women and the second most common female cancer in women aged 15 to 44 years worldwide, with an estimated 604,127 new cases and 341,831 deaths in 2020. Worldwide, cervical cancer mortality rates are substantially lower than incidence, with a mortality ratio of mortality to incidence of 57% (33).

Latin America and the Caribbean are regions with the second highest incidence and mortality after Africa, where coinfection with HIV translates into a higher population risk that adds to deficiencies in access to health services (incidence 14.9 and 25.6 per 100,000 and mortality 17.7 and 7.6 per 100,000, respectively) (33). North America has significantly lower incidence and mortality rates than Latin America and the Caribbean and a lower mortality/incidence ratio (0.34 vs. 0.51, respectively).

The adjusted cervical cancer incidence rate for the Region of the Americas is 11.3 per 100,000, a value three times higher than the elimination goal (four cases per 100,000). There is a significant difference between Latin America and the Caribbean compared to North America, where the respective adjusted rates are 14.9 and 6.1 per 100,000 (33) (Figure 4).

**Figure 4. Estimated age-standardized incidence and mortality rates in 2020 in the Region of the Americas, cervical cancer, all ages.**


**HPV vaccines**

There are six licensed HPV vaccines: Cervarix, Cecolin, Walrinvax (bivalent vaccines), Gardasil and Cevavax (quadivalent vaccines), and Gardasil9 (a nonavalent vaccine) (34). All HPV vaccines are highly immunogenic and have not shown any serious safety issues.
Single dose schedule

Data from immunogenicity trials, post-hoc analyses of efficacy trials, and post-licensure observational studies among females have demonstrated that a single dose of HPV vaccine is sufficient to elicit an immune response that provides similar protection as a multidose regimen against initial and persistent HPV infection. These data include results from a high-quality randomized controlled trial (RCT), which randomized 2250 sexually active 15 to 20-year-old females to receive a bivalent vaccine (Cervarix), a nonavalent vaccine (Gardasil-9), or be part of a control group. (34, 35)

Cervical cancer prevention and control – 90/70/90 global strategy

In response to this reality, the World Health Organization launched a strategy for eliminating cervical cancer as a global public health problem in 2020, which established the goal of reducing the incidence of the disease to less than four cases per 100 000 by 2060. To meet this goal, WHO proposes to achieve 90% vaccination coverage in girls reaching 15 years of age, 70% screening coverage with a high-performance test in women at age 35, and again by age 45. Lastly, to achieve treatment of at least 90% of screen-identified precancerous lesions and invasive cancer (36) (Figure 5).

Figure 5: Global strategy for the elimination of cervical cancer.


PAHO published the Plan of Action for Cervical Cancer Prevention and Control 2018-2030 (37) in September 2018 at the 56th Directing Council, 70th Session of The Regional Committee of WHO for the Americas. The Plan identifies the following four strategic lines of action:

- Improve the organization of cervical cancer programs, governance, information systems, and cancer registries.
- Strengthen primary prevention through information, education, and HPV vaccination.
- Improve cervical cancer screening and precancer treatment through innovative strategies.
- Improve access to cancer diagnosis, treatment, rehabilitation, and palliative care services.
HPV vaccination in the Region of the Americas

Gradually, more countries worldwide have been introducing the HPV vaccine into their national schedules. Forty-seven countries and territories in the Region of the Americas have introduced the HPV vaccine into their national scheme (92% of total countries). The vaccine used is primarily the quadrivalent (Figure 6). In 2022, 27 countries reported that, in addition to girls, they had introduced the vaccine in boys (57% of countries that introduced the HPV vaccine).

Figure 6: HPV vaccine introduction into the Expanded Program on Immunization (EPI), Region of the Americas, April 2023.

As of 2019, the vaccination coverage against HPV falls short of the elimination goal, with only Mexico reporting a coverage rate above 90% with the complete schedule. Canada and Chile achieved 83% coverage, and Peru 76%. In 2021, none of the countries in the Region achieved coverage rates equal to or higher than 90%. The closest to that goal were Canada with 87% and Saint Kitts and Nevis with 84% (Figure 7).

Figure 7. HPV vaccine last dose coverage, Region of the Americas, 2019-2021.


Recommendations on the use of HPV vaccines were issued by the WHO Strategic Advisory Group of Experts (SAGE) on immunization at its meeting in April 2022 (38). WHO subsequently endorsed them in their position paper published in December 2022 (34). SAGE considered the evidence from an updated systematic review on the immunogenicity, efficacy, and effectiveness of single-dose vaccination schedules compared to no-vaccination and multidose schedules.

The review showed comparable efficacy and effectiveness between single and multidose schedules in preventing persistent infection with HPV genotypes 16 and 18, lasting up to 10 years following vaccination. For 9 to 14-year-olds, the review recommends that national immunization programs could use either a single-dose or a two-dose vaccination schedule with an interval between doses of at least six months.

In the Region of the Americas, 11 countries of 47 (23%) have switched to a single dose schedule:

- Anguilla
- Barbados
- Bolivia (Plurinational State of)
- Guatemala
- Guyana
- Jamaica
- Mexico
- Montserrat
- Peru
- Turks and Caicos Islands
TAG Recommendations and Considerations

TAG Recommendations

Recommendations issued by the TAG to the PAHO Director, Dr. Jarbas Barbosa:

1. Countries and territories of the Americas are commended for recognizing the Region’s low vaccination coverage rates against vaccine-preventable diseases (VPDs) and for taking steps to address these serious immunity gaps. Member States are encouraged to continue on the road to recovery by focusing their political, technical, and financial resources on halting and reversing the decline in vaccination coverage for all antigens of the regional immunization program.

2. Polio events or outbreaks must be implemented rapidly (i.e., within 30 days of laboratory confirmation) using an appropriate oral polio vaccine (OPV), and that high vaccination coverage must be achieved through enhanced microplanning, social mobilization, and strategies tailored to reach populations at risk.

3. The recommendation of the SAGE on March 2023 regarding the use of injectable polio vaccine (IPV) to supplement the use of OPV—whether it be novel OPV or Sabin OPV—must be implemented in the Region of the Americas during vaccination campaigns to enhance mucosal immunity and reduce the likelihood of ongoing poliovirus circulation or to close immunity gaps to type 2 polio. However, this strategy must be employed in hard-to-reach areas where immunity gaps are widest or in response to polio events or outbreaks as a strategy to bolster population immunity quickly and effectively. Member States should not delay OPV response operations if IPV vaccine doses are not immediately available.

4. In situations where under-vaccinated communities are in situations of vulnerability or in hard-to-reach areas, polio vaccination operations (including the co-administration of IPV and OPV) should add the administration of all antigens included in the national immunization program for children younger than five years. These operations should include active case search operations for suspected VPD cases in health facilities and in the community. These actions will minimize the risk of new events or outbreaks and reduce viral transmission where an event or outbreak has already occurred.

5. The PAHO Comprehensive Immunization Program should develop a decision-making algorithm to determine which vaccination strategy (OPV alone; OPV and IPV) to use, depending on the epidemiological situation, immunity gaps, affected population, level of community engagement and resources available. Also, PAHO should provide operational guidance to Member States on how to co-administer IPV and OPV.

6. During an event or outbreak, where needed, PAHO staff and international consultants should be rapidly deployed to support Member States during planning and response operations to ensure high-quality vaccination campaigns and high-performing surveillance operations—as was done in pre-pandemic times. This technical cooperation is especially
important when the event or outbreak has occurred in a hard-to-reach area or affects vulnerable populations.

7. Countries should not discontinue the use of bOPV in favor of an IPV-only schedule at this time. Countries that have been classified as "very high risk," "high risk," or "medium risk" for polio by the RCC for at least one of the last three consecutive years should not stop the use of bOPV. It should be noted that many countries in the Region currently fall into this category.

8. Countries and territories of the Americas should use a one-dose vaccination series against HPV if the vaccine product has documented proof of immunogenicity and durable immunity for the one-dose series. Multiple randomized trials and observational studies confirm that the one-dose series (using bivalent, quadrivalent, or nonavalent vaccines) shows comparable immunogenicity, efficacy, effectiveness, and duration of protection as a two-dose series among immunocompetent women ages 18 years or younger at the time of first dose administration. Additional one-dose vaccine products against HPV should be included in this recommendation once their safety and efficacy profiles become available. This recommendation builds upon the statement issued by the SAGE in December 2022 regarding the administration of one or two doses of HPV vaccine to girls aged 9 to 20 years.

9. Countries should ensure that all girls between the ages of 9 and 14 years receive at least one dose of the HPV vaccine. This is in agreement with the SAGE recommendation that immunocompromised individuals or HIV-positive persons (regardless of age or antiretroviral therapy status) should receive at least two doses of HPV vaccine (at a 6-month interval) and, where possible, three doses.

10. Member States should strengthen school-based vaccination programs against HPV since this strategy has been proven to yield high coverage rates. Multiple studies under different field conditions support the implementation, where feasible, of catch-up vaccination for multi-age cohorts (MAC) of girls aged 9 to 18 years. since this results in a faster and greater population impact due to increased direct and herd protection. Given the ample supply of moderately priced HPV vaccine doses available to the Americas through the Revolving Fund, HPV vaccination should be offered to women aged 15 years or older, immunocompromised persons of all ages, and boys. This recommendation would close the immunity gaps generated during the COVID-19 pandemic because of school closures.

11. Vaccination services against HPV should be fully integrated within a comprehensive approach towards cancer prevention to achieve the goal of global cervical cancer elimination. This integration involves primary prevention of HPV infection through immunization and secondary prevention through early detection of HPV infection for women aged 35 to 45 years.

12. PAHO should lead the implementation of a multi-country cost-effectiveness study on the introduction of whole-cell Pertussis (wP) hexavalent vaccine in the Americas before doses become widely available on the global market. The results will help Member States make informed decisions regarding the age groups to target and the vaccination platforms to use.
TAG Considerations

These considerations do not carry the same weight as TAG recommendations because they are based on a smaller body of evidence. Nonetheless, to support the negotiations of the Revolving Fund with pharmaceutical companies in the production of hexavalent vaccine doses, the TAG issued these considerations to the PAHO Director, Dr. Jarbas Barbosa, for his review:

1. Member States are encouraged to consider the introduction of the whole-cell pertussis (wP) hexavalent vaccine in the national immunization programs of the Americas. Combined vaccines such as the hexavalent are a key tool to bolster regional vaccination coverage rates, improve the logistics of vaccine transportation, storage, and administration, and reduce medical waste. Furthermore, multiple studies support its non-inferiority status to acellular pertussis (aP) hexavalent vaccine, and the reactogenicity profiles of the two vaccines are similar. Finally, the wP hexavalent vaccine provides longer duration of immunity than the aP hexavalent vaccine. Countries that already use the aP hexavalent vaccine should continue to do so.

2. In July 2021, countries and territories were recommended a five-dose vaccination series against polio (three doses in the primary series and two booster doses), using a combination of IPV and bivalent OPV doses.

<table>
<thead>
<tr>
<th>Vaccination schedule</th>
<th>Primary series</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 2021</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
</tr>
<tr>
<td>2 months</td>
<td>IPV</td>
<td>bOPV</td>
</tr>
<tr>
<td>4 months</td>
<td>12-18 months</td>
<td>4-5 years</td>
</tr>
</tbody>
</table>

Considering the forthcoming availability of the wP hexavalent vaccine, Member States should consider a revised vaccination schedule that incorporates this vaccine into the national immunization schedule without disruptions or the need for additional training. This proposed schedule also uses five doses (three doses in the primary series and two booster doses) for the same age groups but replaces IPV with the wP hexavalent vaccine and adds one dose of the wP hexavalent vaccine as a booster.

<table>
<thead>
<tr>
<th>Vaccination schedule</th>
<th>Primary series</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 2023</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
</tr>
<tr>
<td>2 months</td>
<td>Hexavalent</td>
<td>Hexavalent + bOPV</td>
</tr>
<tr>
<td>4 months</td>
<td>12-18 months</td>
<td>4-5 years</td>
</tr>
</tbody>
</table>

3. The Revolving Fund should continue its proactive negotiations to ensure enough vaccine doses at competitive prices for Member States, especially considering the expected limited global supply of wP hexavalent vaccine doses worldwide until at least 2027. Countries and
4. The PAHO Comprehensive Immunization Program should work closely with Member States on the introduction of any WHO-prequalified wP hexavalent vaccine as soon as it becomes available and consider how the addition of this vaccine to the national immunization program may affect routine vaccination services as well as the introduction of other new vaccines (e.g., RSV, dengue). Also, PAHO should support countries in the integration of the wP hexavalent vaccine into the national surveillance systems for Events Supposedly Attributed to Vaccination or Immunization (ESAVI).
References


