Review of experience and usage modalities of IPV-containing vaccines

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Some key characteristics of OPV are challenging the eradication of the circulation of polioviruses and control of paralytic poliomyelitis

- The by-dose and by-serotype SC in vaccinees is not consistent and low in many settings and the by-dose (and cumulated) vaccine effectiveness is sub-optimal despite vaccination programs relying on > 10 consecutive OPV administrations up to 5 years of age
  - Host-related: concomitant viral, bacterial or parasitic enteric infections
  - Vaccine-related: intra-vaccine viral interference (type 2 the best replicant +++)
  - Environment-related: prevalence of maternally-transmitted Abs and breast-feeding
  - Investigations / hypothesis
    - Post-birth short-lived inhibitory factors in some ethnicities / settings
    - The gut microbiome
- The use of mOPV₁, mOPV₃ and bOPV₁&₃ do improve the immune responses against polioviruses types 1 and 3, and therefore do improve their effectiveness
Vaccine-Derived Polioviruses (VDPV): an inevitable consequence of the suboptimal use of OPV

- VDPV are polioviruses presenting more than 1% genomic divergence from the parental Sabin poliovirus in their VP1 sequence (0.6% for type 2)
  - Accumulation of mutations (1% nucleotide change /yr) or recombinations with other enteroviruses in the genomes of circulating Sabin virus within the vaccinee’s gut or within vaccinee’s contacts’ gut
  - When detected, prove that such virus lineage circulates since at least one year
  - Reverted to neurovirulence (or paralyticogenicity) and transmissibility

- cVDPV (circulating VDPV) is a VDPV responsible for at least 2 AFP cases
  - Low vaccination coverage
  - Poor sanitation conditions
  - High population density
  - Lack of competition from WPV circulation
  - Tropical conditions
Since 2000, 23 cVDPV outbreaks (14 type 2; 6 type 1; 3 type 3) have been responsible for ~ 700 AFP cases - 7 outbreaks still active in 2013 -

http://www.polioeradication.org/Dataandmonitoring/Poliothisweek.aspx
Points to consider when choosing between OPV-only, IPV-only, mixed/combined use of OPV and IPV or IPV-followed-by-OPV sequential regimens (1/2)

• Risks for sustained circulation of polioviruses within communities
  – Mode of PV transmission: faecal-to-oral and / or oral-to-oral
  – Sewage equipment level / sanitation / hygiene
  – Potential for PV importations

• NIP performance
  – Number of established routine vaccination opportunities
  – By-dose coverage rate for the DTP-backboned vaccines
  – Existence of pockets of uncovered populations
  – Feasibility and willingness to rely on SIAs (NIDs and / or SNIDs)
Points to consider when choosing between OPV-only, IPV-only, mixed/combined use of OPV and IPV or IPV-followed-by-OPV sequential regimens (2/2)

• Desire to eliminate VAPP occurrence
  – Immunizing after birth (≥6 weeks) with IPV (≥1 dose) is a way to eliminate VAPP

• Accessibility to IPV-containing vaccines
  – Affordability of the products
  – Presence of national manufacturer(s)
  – Reliability of the supply from manufacturer(s)
  – Role of NRA in defining the licensing rules
  – Role of National Advisory Committees on Immunization Policies
IPV-containing vaccines have demonstrated excellent and consistent immunogenicity profiles irrespective of conditions of use

- More than 300 pre- and post-licensure clinical trials or intervention studies in more than 50 countries (including tropical) since 1977 with various IPV-containing products (15)
- In primary immunization in infant / toddlers
  - IPV-only regimen
  - IPV-followed-by-OPV sequential regimen
  - IPV-only regimen supplemented by OPV SIAs
  - Mixed / Combined use of IPV and OPV regimen
  - OPV-followed-by-IPV sequential regimen
  - All these regimens with or without OPV at birth
- As a polio immunity booster in pre-school children, adolescents, adults and the elderly
- As a polio immunity “priming” vaccine in adolescents and adults with unknown or variable vaccination histories
- In special populations: HIV+, bone-marrow transplanted, pre-terms

IPV-containing products do induce immunological priming after first dose

- One single IM IPV dose in naive 4-month old infants seroconverts 32%-63% (all types)
- 97%-98% of infants who didn't seroconvert after single IPV dose evidenced immunological priming (against all types)

Resik S & al. NEJM 2013
IPV-containing products do induce seroconversion and seroprotective levels in almost all subjects after two doses

- The TPP of modern IPV: a formulation sufficiently immunogenic when given 2 times with a relative long interval (6 months) in developing countries
- High immunogenicity after 2nd dose: In 30 trials involving >4500 subjects, seroprotection against poliovirus
  - 89-100% against type 1
  - 92-100% against type 2
  - 70-100% against type 3

Vidor E & al. PIDJ 1997;16:312-322
Two doses of IPV during the first year of life are able to reduce prevalence, intensity and duration of intestinal PV excretion following infection (OPV challenge) compared to 1st time OPV-recipients

Viral shedding of any type after different schedules of vaccination with oral poliovirus vaccine (OPV) and inactivated poliovirus vaccine (IPV).

<table>
<thead>
<tr>
<th>Vaccination schedule (dose selected for shedding follow-up)</th>
<th>1 week after the most recent dose of OPV</th>
<th>3 weeks after the most recent dose of OPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tested, no.</td>
<td>PCR positive, no. (% [95% CI])</td>
</tr>
<tr>
<td>OPV (first dose)</td>
<td>48</td>
<td>44 (92 [0.00-98])</td>
</tr>
<tr>
<td>IPV (first dose)</td>
<td>12</td>
<td>0 (0 [0.00-25])</td>
</tr>
<tr>
<td>OPV/IPV/OPV (third dose)</td>
<td>41</td>
<td>9 (22 [11-88])</td>
</tr>
<tr>
<td>IPV/IPV/OPV (third dose)</td>
<td>42</td>
<td>32 (76 [41-88])</td>
</tr>
</tbody>
</table>

**NOTE.** CI, confidence interval; PCR, polymerase chain reaction.
Three-doses infant primary series regimen immunogenicity is the best performer in terms of circulating poliovirus neutralizing Abs

% of infants with post-dose 3 detectable antibodies

Vidor E & al. PIDJ 1997;16:312-322
Multiple factors drive the immunogenicity of IPV-containing vaccines when used for infant primary immunization

- Number of primary series injections ($2 < 3$)
- Age at first injection (younger [6 weeks of age] < older [3 months or later])
- Interval between doses (1 month < 2 months < more than 2 months)
- Ecological context (presence of passively transmitted Abs)
- Presence of an aluminium salt adjuvant in the vaccine formulation (standalone un-adsorbed IPV < IPV-containing adjuvanted multivalent combination products)
Different IPV-followed-by-OPV sequential regimens have been documented

• 14 trials done with several types of IPV-containing vaccines in 8 countries since 1986
  – USA (5), China (3), France, UK, Brazil, Mexico, Taiwan & Guatemala
• 1 or 2 IPV followed by 1 or 2 OPV administered as 2+1, 3+1 or 3+0 regimen
• No OPV given at birth
• Several types of study design
  – Non-randomized descriptive-only licensing or launch studies or RCTs between sequential schedules and IPV-only and / or OPV-only schedules
  – Some trials have investigated prevalence, intensity, duration and genetics of PV excretion after OPV vaccination / challenge
• Several types of IPV-containing vaccines
  – IPV standalone (Vero IPV or MRC₅ IPV)
  – wP-based combinations
  – aP-based combinations
As of Oct 2013 ~70 countries have introduced IPV in their routine National (Infant / Toddler / Children) Immunization Programs.


Apart IPV-only regimen, a multitude of routine polio immunization regimen can be implemented

- **IPV-only supplemented by OPV SIAs**
  - Mexico: IPV at 2, 4, 6 and 15-18 months of age completed by OPV NIDs twice a year in all <5yrs

- **Mixed / combined use of IPV and OPV with OPV optional at birth**
  - Turkey: IPV at 2 and 4 months, and IPV & OPV at 6 and 18 months
  - South Africa: OPV at birth, IPV & OPV at 6 weeks, IPV at 10, 14 weeks and 18 months + OPV triennial SIAs (NIDs) in all <5yrs

- **IPV-followed-by-OPV**
  - US (from 1997 to end of 1999): IPV at 2 and 4 months and OPV at 6 to 18 months and at 4 – 6 years
  - Russia: IPV at 3 and 4.5 months and OPV at 6, 18 and 20 months
  - Brazil (since 2012): IPV at 2 and 4 months and OPV at 6 and 15 months + OPV SIAs

- **OPV-followed-by-IPV**
  - SAGE recommendation for LICs and LMICs
    - At least one dose of IPV following OPV at time of DTP#3
  - Not yet implemented
IPV-followed-by-OPV regimen is the most relevant from a Public Health perspective in polio-afflicted communities

- Address the VAPP issue
- Combine the full benefit of both vaccines in terms of breath of individual responses (mucosal and humoral)
- The incorporation of at least one dose of IPV at the start of the immunization schedule increase post-primary series Ab levels compared to OPV-only schedules
- A 3-dose IPV-IPV-OPV primary series regimen during the 1st year of life is the best performer in terms of post 3-dose antibody levels (versus OPV-only)
- Two doses of IPV during the 1st year of life schedule is able to reduce prevalence, intensity and duration of PV excretion following an early OPV vaccination / challenge compared to 1st time OPV-recipients
- The use of OPV in populations where exists pockets of uncovered will allow their "indirect vaccination" if environmental / ecological conditions are adequate
WHO is still viewing OPV as the main tool for polio eradication, but is now considering IPV in the end game strategy

• The total number of AFP cases due to WPV will be lower than those due to VDPVs and VAPP

• To that end, WHO is strongly pushing for affordable IPV options
  – Reduced Ag delivery: the IPV ID administration
  – Sabin strain-derived or genetically-stabilized Sabin strain-derived IPV
  – Newly adjuvanted IPV vaccine lowering the Ag needs
  – Reduced schedule: 2-dose
  – wP-IPV hexavalent combinations

• Will be the type 2 PV protection provider when the tOPV-to-bOPV$_{1&3}$ switch will be effective

• All WHO-advisory bodies (SAGE Polio WG, PRC, ACPE, IMB) and external stakeholders (BMGF, CHAI, GAVI, PATH) now have IPV in mind
SAGE recommendation: at least 1 dose of IPV in routine schedule and IPV for outbreak control - To be updated before year end -

SCHEDULE:

SAGE Working Group draft recommendations*:

- 6, 10, 14 weeks or 2, 3, 4 months schedule: add IPV dose at the DPT3 contact;

- 2, 4, 6 months schedule: add IPV dose at the DPT3 contact, though DPT2 can be considered;

- countries with documented VAPP risk prior to 6 months of age may decide to consider alternative schedules

* for current OPV-only countries; the WG is not recommending to change existing schedules
From all the experience and data accumulated through clinical trials, introduction programs and routine use of IPV-containing vaccines over 35 years, it is Sanofi Pasteur’s conviction that …

- Every opportunity of catching 0 to 2 years old infants living in LICs and LMICs should be used to administer IPV to them with a 2-dose IPV-only IM-dosing regimen whatever the number and type of OPV administered before, during or after these IPV dosing opportunities
- All OPV dosing done on the top of this minimal IPV regimen will
  - maximize the vaccination coverage in polio-afflicted communities if ecological conditions permit
  - re-enforce the quality of humoral and mucosal immunity of vaccinees, and therefore will decrease their role in the chain of poliovirus transmission
Conclusions

- OPV limitations drive the need for evolution
- Multiples drivers govern the choice of the polio immunization regimen to be used in each situation
- A large and diverse experience has been accumulated with IPV-containing vaccines
- Many countries have already adopted IPV with different approaches in terms of immunization regimen
- Role of IPV will be key in the end game strategy of the WHO driven GPEI
- A 2-dose IPV-only IM-dosing regimen should be the backbone of all polio immunization regimens