IPV introduction & OPV2 withdrawal
Regulatory implications

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International workshop on Quality management Systems for validation of changes in vaccine manufacturing
DCVMN meeting, Mexico City, 10-11 July 2013
Presentation overview

• Current status of eradication
• Strategic Plan 2013-2018
  – Sequential removal of OPV (commencing with OPV2) & introduction of a routine dose of IPV
  – Recent recommendations by SAGE WG on Polio
• Issues surrounding policy changes
  – Vaccine use, availability, & uptake
  – Recent GAVI board decision
• Regulatory implications
• Next steps
Current status of eradication
Polio, type 3 cases globally

The last WPV3 case reported had onset in November 2012 in Nigeria.
## Wild Poliovirus, Previous 6 Months*

*03 January – 02 July 2013

- Wild virus type 1

<table>
<thead>
<tr>
<th>Country</th>
<th>Onset of most recent case</th>
<th>Number of Districts</th>
<th>Virus Type</th>
<th>TOTAL WPV</th>
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</thead>
<tbody>
<tr>
<td>Kenya</td>
<td>03-Jun-13</td>
<td>2</td>
<td>7</td>
<td>7</td>
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<tr>
<td>Nigeria</td>
<td>18-May-13</td>
<td>18</td>
<td>26</td>
<td>26</td>
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<tr>
<td>AFR Total</td>
<td>03-Jun-13</td>
<td>20</td>
<td>33</td>
<td>33</td>
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<tr>
<td>Afghanistan</td>
<td>06-Jun-13</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Pakistan</td>
<td>06-Jun-13</td>
<td>10</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Somalia</td>
<td>03-Jun-13</td>
<td>17</td>
<td>41</td>
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<tr>
<td>EMR Total</td>
<td>06-Jun-13</td>
<td>30</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>06-Jun-13</strong></td>
<td><strong>50</strong></td>
<td><strong>95</strong></td>
<td><strong>95</strong></td>
</tr>
</tbody>
</table>

Data in WHO HQ as of 02 July 2013
Polio Paralyzed Children, last 6 months

- no type 3 globally
- 50% decline in endemic cases vs 2012
- HoA re-infected & 50% of global cases
- EGY, ISR +ve sewage
cVDPV active outbreaks, last 6 months

- cVDPV2 (13 cases)
- cVDPV1 (0 cases)
- cVDPV3 (0 cases)
The highest risk: cVDPV outbreaks, 2000-2013

14 countries have had type 2 cVDPV

Type 1 (79 cases)
Type 2 (572 cases)
Type 3 (11 cases)
Polio Eradication & Endgame
Strategic Plan 2013-2018
In May 2012, the WHA declared the completion of poliovirus eradication to be a programmatic emergency.

In response, the polio eradication and endgame strategic plan 2013-2018 was developed by the Global Polio Eradication Initiative and partners.
What are the 4 objectives of the new endgame strategy?

- Detect and interrupt poliovirus
- Strengthen immunizations systems and withdraw OPV
- Contain and certify
- Plan polio's legacy
Endgame Major Objectives

**Virus detection & interruption**
- **2013**: Wild virus interruption
- **2014**: Outbreak response (esp. cVDPVs)
- **2015**: RI strengthening & OPV2 pre-requisites
- **2016**: Introduce IPV
- **2017**: OPV2 withdrawal
- **2018**: Finalize long-term containment plans

**RI strengthening & OPV withdrawal**
- **2013**: RI strengthening & OPV2 pre-requisites
- **2014**: Introduce IPV
- **2015**: OPV2 withdrawal
- **2016**: Complete containment & certification globally
- **2017**: Consultation & strategic plan
- **2018**: Initiate implementation of legacy plan

**Containment & certification**
- **2013**: Finalize long-term containment plans
- **2014**: Complete containment & certification globally
- **2015**: Consultation & strategic plan
- **2016**: Initiate implementation of legacy plan
- **2017**: Consultation & strategic plan
- **2018**: Consultation & strategic plan

**Legacy Planning**
- **2013**: Consultation & strategic plan
- **2014**: Initiate implementation of legacy plan
- **2015**: Consultation & strategic plan
- **2016**: Consultation & strategic plan
- **2017**: Consultation & strategic plan
- **2018**: Consultation & strategic plan

**Timeline**
- **2013**: Last wild polio case
- **2014**: Last OPV2 use
- **2015**: Certification
What is the new endgame approach to immunization policy?

- **Sequential** cessation of oral Sabin vaccine strains, starting with Sabin type 2.
- **Replacing** tOPV with bOPV in a synchronized manner globally as the first step in OPV cessation.
- **Mitigating risk** by including at least one dose of IPV in the routine EPI in addition to OPV (starting ≥6 months before switch from tOPV to bOPV).
Why is this strategy needed?

OPV is a live attenuated vaccine which, in rare occasions, can cause paralytic disease in two main ways:

• Vaccine associated paralytic poliomyelitis (VAPP) due to a reversion of the vaccine virus to neurovirulence, 250-500 cases globally per year, 40% due to type 2;

• Circulating vaccine derived poliovirus (cVDPV) outbreak due to mutation of the virus by passage from person to person mainly caused by type 2 in recent years.
In 1992, single-dose IPV at 3 mos before OPV

In 2006, IPV-only schedule

One IPV dose prevents VAPP in Hungary
VAPP

• Efficacy of a single IPV dose (3-mos) before OPV prevented 100% VAPP (Hungary)

• Epidemiology of VAPP is different in developing countries (India, Iran)
  – OPV immunogenicity lower
  – age at VAPP onset higher (mostly associated with subsequent OPV dose, not first dose)
  – maternally-derived antibody protect young infants
  – total annual VAPP risk estimated at 2-4 cases per birth cohort (TCG 2002)

• Fraction preventable with early administration of IPV could be quite small (~10%)
What will these policy changes achieve?

• proactively address Sabin type 2 burden of paralytic disease (VAPP & cVDPV)

• ensure the gains of eradicating WPV2 forever while still pursuing the eradication of WPV1 & 3

• provide potential additional benefits
  – accelerate eradication of WPV1 & 3 by boosting type 1 and 3 immunity with bOPV & IPV
  – provide lessons for cessation of all Sabin virus at a time when stakes are lower
What is the rationale for introducing a routine dose of IPV prior to OPV2 cessation?

- **Mitigate the risks of outbreak** if VDPV2 or WPV2 is re-introduced after OPV2 is stopped
  a) reduce transmission
  b) prevent individual cases of polio
  c) provide priming to rapidly improve response to mOPV2 in an outbreak

- **Boost immunity** to WPV1 & 3
SAGE 11/2012: Decision to recommend at least 1 dose of IPV into routine schedules (risk mitigation)
IPV schedule options

- **Main routine schedules:**
  - **EPI:** DTP at 6, 10 and 14 weeks
  - **PAHO:** DTP at 2, 4, and 6 months
  - **China & Indonesia:** DTP at 2, 3, and 4 months
- Additional contacts:
  - OPV/BCG at birth
  - Measles at 9 months or later

- **Schedule**

  Birth  6  10  14  >9

Question: At which DTP dose to add a supplemental IPV dose?
Poliovirus types 1+3 considerations

- A schedule with 3-4 OPV + 1 IPV will largely close the immunity gaps to types 1+3
- IPV at DTP3 contact implies at least 2 previous OPV doses (necessary for optimal mucosal immunity)
- IPV boost mucosal immunity very effectively in previously OPV vaccinated individuals

Modlin J et al. JID 1997;175:S228-S234.
Early vs. later IPV administration

**IPV at 4-months:** 63% seroconversion, 98% priming

**Later dose (>4 mos):** no evidence of seroconversion/priming gain

**Earlier dose (2 mos):** seroconversion falls to 35%; priming <90%

<table>
<thead>
<tr>
<th>Author year (ref)</th>
<th>Country</th>
<th>Schedule</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>McBean 88 [45]</td>
<td>US</td>
<td>2 mo</td>
<td>35%</td>
</tr>
<tr>
<td>Simasathien 94 [46]</td>
<td>Thailand</td>
<td>2 mo</td>
<td>39%</td>
</tr>
<tr>
<td>Resik 10 [40]</td>
<td>Cuba</td>
<td>6 wk</td>
<td>36%</td>
</tr>
<tr>
<td>Mohammed 10 [47]</td>
<td>Oman</td>
<td>2 mo</td>
<td>32%</td>
</tr>
<tr>
<td>Resik 13 [39]</td>
<td>Cuba</td>
<td>4 mo</td>
<td>63%</td>
</tr>
</tbody>
</table>
SAGE Working Group May 2013 draft recommendations on schedule for IPV*:

- 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 < 6 months of age may consider alternative schedules

* for current OPV-only countries; the WG is not recommending to change existing schedules
Issues surrounding immunization policy changes
Prerequisites for OPV2 cessation:

- Validation of persistent cVDPV2 elimination & wild poliovirus type 2 eradication
- Stockpile of mOPV2 and response protocol & capacity
- Surveillance and international notification of Sabin, Sabin-like and cVDPV type 2
- Licensed bOPV available in all OPV-using countries
- Affordable IPV option for all OPV-using countries
- Containment phase II for cVDPV2 and wild poliovirus type 2 and phase I for Sabin type 2
Issue: 125 'OPV-only' countries

- IPV ONLY (47 countries)
- IPV/OPV (18 countries)
- OPV ONLY (125 countries)
Issue: DTP3 coverage $\leq 80\%$, 2009-11

- $\geq 80\%$ (151 countries or 77%)
- $< 80\%$ (43 countries or 23%)
- Not available
SAGE Working Group:
Countries could be prioritized (tiered) for IPV introduction based on cVDPV risk
Tier 1: WPV endemic + cVDPV2 emergence
Tier 2: cVDPV1/3 emergence or low DPT3 for 3 years
Tier 3: Low DPT3 for at least one recent year
Tier 4: Other OPV only using countries
**GAVI Board Decision (12 June):**

- play lead role for IPV intro in 73 GAVI countries
- immediately communicate importance of IPV
- establish finance/supply strategy with GPEI by November 2013
- request donors to ensure financing
IPV & bOPV introduction
Regulatory implications
## Status of prequalified OPV

<table>
<thead>
<tr>
<th>Company</th>
<th>tOPV</th>
<th>bOPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK, Belgium</td>
<td>29 March 2004</td>
<td>29 October 2009</td>
</tr>
<tr>
<td>Sanofi Pasteur, France</td>
<td>16 June 2002</td>
<td>2 August 2011</td>
</tr>
<tr>
<td>Bio Farma, Indonesia</td>
<td>9 April 1997</td>
<td>26 May 2010</td>
</tr>
<tr>
<td>Novartis, Italy</td>
<td>2 January 1987</td>
<td>10 November 2011</td>
</tr>
<tr>
<td>Haffkine, India</td>
<td>2 February 2006</td>
<td>19 March 2010</td>
</tr>
<tr>
<td>SIIL, India</td>
<td>2 April 2013</td>
<td>4 January 2013</td>
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## Status of prequalified IPV

<table>
<thead>
<tr>
<th>Company/Institution</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilthoven Biologicals (NVI), Netherlands</td>
<td>6 December 2010</td>
</tr>
<tr>
<td>GSK, Belgium</td>
<td>5 August 2010</td>
</tr>
<tr>
<td>Sanofi Pasteur, France</td>
<td>9 December 2005</td>
</tr>
<tr>
<td>Statens Serum Institut, Denmark</td>
<td>23 December 2010</td>
</tr>
<tr>
<td>Fillers of inactivated trivalent bulks</td>
<td>In the pipeline</td>
</tr>
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</table>
Regulatory priorities: Product introduction & use

• **Immediate priorities**
  – *IPV*
    • Multi-dose presentation (5 or 10 doses) → implications for cold chain requirements, production capacity and cost
    • IPV given in addition to OPV/bOPV → booster/priming dose with seroprotection to be documented by clinical data
  – *bOPV1&3*
    • Label change for routine use → seroprotection to be documented by clinical data
Regulatory priorities: Product introduction & use

• **Next priorities**
  – Label change for intradermal delivery of IPV (e.g. needle&syringe, needle-free device, micro-needles patch

• **Final priorities**
  – Regulatory approval for bOPV and IPV where necessary
Regulatory meeting

• 26 July 2013, meeting convened in Geneva with NRAs of prequalified OPV/IPV

• The main objective is
  
  – to define regulatory pathway and requirements needed to change indications of use of bOPV and IPV

  – Regulatory pathway and requirements for the licensing of IPV given by ID route and adjuvanted formulation
Objective 2A

bOPV Label Change from campaign only use to Routine use in a Primary Series Schedule (6, 10, 14 wk)

Regulatory Requirement:
Data demonstrating equivalence of bOPV to tOPV for types 1 and 3 seroconversion (data for each bulk supplier)

India Comparison of all bOPVs versus tOPV given at 0 and 4 wks
- 2 Panacea tOPV (0, 4 wks)
- 2 Panacea – Sanofi bOPV (0, 4 wks)
- 2 Haffkine – Bio Farma bOPV (0, 4 wks)
- 2 Bharat – Bio Farma bOPV (0, 4 wks)
- 2 Bio Farma bOPV (0, 4 wks)
- 2 GSK bOPV (0, 4 wks)
- 2 Sanofi bOPV (0, 4 wks)
- 2 Novartis bOPV (0, 4 wks)
- 2 SII bOPV (0, 4 wks)

Bangladesh Short Interval: Immunogenicity of Oral Polio vaccines provided at different intervals
- 3 GSK bOPV 6, 10, 14 wks (n=200)
- 3 Sanofi tOPV (6, 10, 14 wks) n=259
- 2 BB/SII IPV Full dose IM (6, 14 wks) n=194
- 2 BB/SII IPV Fractional dose ID by nano-pass (6, 14wks) n=259
- 2 bb/SII IPV Fractional dose ID by nano-pass (6, 14wks) + Sanofi bOPV (10wks) n=259

Pakistan Short Interval Study
- 1 GSK tOPV (0wks) + bOPV (6, 10, 14 wks) n=200

*Might be relevant in understanding type-2 immunity after 1 dose tOPV plus bOPV.

Objective 2B

bOPV Primary Series + IPV for boosting type 1 and 3 Immunity and priming type 2 Immunity

Regulatory Requirement:
Non-inferiority manufacturer specific data for Full Dose and fractional dose:
1. Response rate positive after dilution 1/8
2. Delta margin of 5%
3. At least 95% responders for types 1 and 3
4. At least _% responders for type 2

India EPI Study: Immunogenicity of bOPV, tOPV, bOPV/IPV, and tOPV/IPV schedules
- 4 Panacea tOPV (0, 6, 10, 14 wks) n=180
- 4 Panacea tOPV (0, 6, 10, 14 wks) + 1 Panacea IPV full dose (14 wks) n=180
- 4 Panacea tOPV (0, 6, 10, 14 wks) + 1 Panacea IPV Full dose IM (9m) n=180
- 4 Panacea tOPV (0, 6, 10, 14 wks) + 1 BB/SII IPV Full Dose IM (14wks) n=50
- 4 Panacea tOPV (0, 6, 10, 14 wks) + 1 Sanofi IPV Full Dose IM (14wks) n=50

Latin America Full Dose IPV IM boosters in bOPV primed Infants
- 3 Sanofi bOPV (6, 10, 14 wks) n=210
- 3 Sanofi tOPV (6, 10, 14 wks) n=100
- 3 Sanofi bOPV (6, 10, 14 wks) + 1 Sanofi IPV Full Dose IM (14wks) n=210
- 3 Sanofi tOPV (6, 10, 14 wks) + 1 Sanofi IPV Full Dose IM (9m) n=210
- 3 Sanofi bOPV (6, 10, 14 wks) + 1 BB/SII IPV Full Dose IM (9m) n=190
- 3 Sanofi bOPV (6, 10, 14 wks) + 1 GSK IPV Full Dose IM (14wks) n=50
- 1 GSK IPV Full Dose IM (9m) n=190

WHO

WHO Panning

BMGF

Bulk
<table>
<thead>
<tr>
<th>Filler</th>
<th>GSK</th>
<th>Sanofi</th>
<th>Panacea</th>
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<tbody>
<tr>
<td>tOPV EPI</td>
<td>Bangla. Short Interval n=200</td>
<td>Latin America n=100</td>
<td>Bangla. fIPV n=259</td>
<td>India bOPV Com</td>
<td>India EPI n=180</td>
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<tr>
<td>bOPV EPI</td>
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Table:

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<th>GSK</th>
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<th>BB/SII</th>
<th>Panacea</th>
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<tbody>
<tr>
<td>bOPV Primary Series + IPV IM Full dose (14wks)</td>
<td>Latin America n=50</td>
<td>Latin America n=210</td>
<td>Latin America n=50</td>
<td>India EPI n=180</td>
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<tr>
<td>bOPV Primary Series + IPV ID fractional Dose by Needle &amp; Syringe (14wks)</td>
<td>Latin America n=50</td>
<td>Bangla. fIPV n=259</td>
<td>Latin America n=210</td>
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<tr>
<td>Other bOPV + IPV Schedules</td>
<td>Latin America n=210</td>
<td>Bangla. fIPV n=259</td>
<td>Latin America n=210</td>
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</table>
4A: Alum Adjuvanted Vaccine for BOOSTING

Objective 1: ID Label Change for Booster Dose

- WHO ID Label Change (Thailand? Indonesia?)

Objective 2: bOPV

2A: bOPV Label Change from Campaign → Primary

- WHO Pakistan Short Interval
- CDC Bangladesh Short Interval
- CDC Bangladesh fIPV
- WHO India EPI
- WHO bOPV Comparison

2B: bOPV Primary Series + IPV

- WHO India EPI
- BMGF Latin America bOPV + IPV boost

Objective 3: ID Device Approval

3A: ID Device Approval for IPV as a booster in OPV primed

- WHO Device Comparison in Cuba Sanofi IPV
- ID Device Vaccine Pair Study
- BMGF Study in The Gambia

3B: ID Device Approval for IPV Primary Series in EPI

No ongoing or planned studies

Objective 4: Approval Alum Adjuvanted Salk IPV

4A: Alum Adjuvanted Vaccine for BOOSTING

- Accelerated: Preclinical/Phase I → Phase II/III → Licensure
- Regular: Preclinical and Phase I → Phase II/III

Safety Licensure
Next steps
<table>
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<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>11/2013</td>
<td>SAGE recommendations on IPV schedules, draft response protocol, draft IPV supply and financing strategy</td>
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<tr>
<td>5/2014</td>
<td>WHA information paper and possible technical briefing on OPV2 withdrawal</td>
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<tr>
<td>11/2014</td>
<td>SAGE recommendation on final response protocol and potential target date for last OPV2 use</td>
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<tr>
<td>5/2015</td>
<td>WHA resolution on key OPV2 withdrawal issues</td>
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Summary

• The Strategic Plan 2013-18 has implications for immunization policy potentially within the next 3 years
  – *Cessation of OPV2 (tOPV/bOPV switch)*
  – *Introduction of a routine dose of IPV in OPV-only countries*

• The intention is to address Sabin type 2 burden of disease (VAPP & cVDPV) & to secure the gains of eradicating WPV2 forever

• IPV introduction as a risk mitigation strategy can be tiered based on risk

• There are still issues that need to be addressed & questions that need to be answered in finalizing policy
Thank you for your attention