Sabin-IPV technology and the role of DCVM’s in IPV supply

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Developing Countries Vaccine Manufacturers Network (DCVMN), September 15-16, 2010 in Hyderabad, India.

**Agenda**

- **Introduction to NVI**
  - Changes in NVI’s national legal status (transition)
  - Impact on (Sabin)-IPV technology

- Vaccine choice: pre- and post-eradication era

- WHO’s commitment to develop affordable polio vaccine

- Sabin-IPV Vaccine Project

- Summary
Introduction to NVI

Mission:

Protection of the Dutch population against infectious diseases through the supply of sufficient, high-quality vaccines both under normal and special circumstances.
Introduction to NVI

Core tasks:

• Supplying high quality and affordable vaccines through production or procurement
• Research and development of vaccines
• Ensuring scientific knowledge on vaccinology and vaccination strategies for the ministry of Health
Introduction to NVI


‘The NVI’s vaccine production tasks will be privatized, and there will be a stronger focus on the procurement, storage and distribution of vaccines and on research and development’.
a) Production facilities and services will be privatized

‘ All current contracts between the NVI and third parties will of course be honored, including the contract with the WHO regarding (Sabin)-IPV project ’.

Privatization process to be started September 2010
Introduction to NVI

b) Support functions (QC, QA ….etc) will, in principle, also be privatized

‘Since these services also support public research and development activities, the provision of services to the government must be guaranteed. Here, too, existing contracts with the third parties will be honored ’.

Privatization process to be started in 2011
c) Public vaccine functions will be integrated within a reorganized RIVM

‘........integrated implementation within a single organization will optimally strengthen the public tasks’

Integration will start January 2011 and be functional by January 2012
Public Vaccine functions integrated in RIVM departments and expertises

Vaccinology

Acces to Animal Facility & Pilotplant (GMP)

Vaccin Research
- Virology
- Bacteriology
- Immunology
- Bio-organical chemistry

Process Development
- US & DS Processing
  - Scale up validation
  - Process transfer
- ‘Omics’

Formulation & Analytical Research
- Immunochemistry
  - Protein characterisation
  - ‘Omics’
- Vaccinadministration
  - Vaccininstabilisation

Clinical & Regulatory Research
- Clinical studies
- Knowledge guidelines & directives
- Knowledge of registration

Knowledge & Technology transfer

& Procurement

Storage & Distribution

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New Vaccine Idea

VR vaccine research
PD process Development
FAR formulation & Analytical research
CRR clinical and regulatory research

For TT projects (pre)clinical testing will be initiated/ conducted

Antigen characterization
Small scale process development
Clinical phase I, II
Scale up & process validation
Clinical phase III
Consistency batches registration

Technology Transfer

Market Production

Process Development Focus

VR
PD
FAR
Production QC, QA, CR
PD
Production QC, QA
Registration

Introduction to NVI
Introduction to NVI

Salk-IPV production will be privatized

- Existing supply agreements will be honored

Sabin-IPV project will remain in the public domain

- Transfer of Sabin-IPV technology to potential partners will start in 2011
<table>
<thead>
<tr>
<th>Project</th>
<th>Vaccine(s)</th>
<th>Recipient</th>
<th>Country</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Micro-carrier technology (1970-1980)</strong></td>
<td>Viral vaccines</td>
<td>Sanofi, GSK, Sclavo (Novartis)...</td>
<td>Several</td>
<td>Turn-key</td>
</tr>
<tr>
<td>WHO Course on Laboratory methods for titration of Live Virus Vaccines</td>
<td>OPV en Measles</td>
<td></td>
<td>Egypt</td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td></td>
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</tr>
<tr>
<td>China Vaccine Project, World Bank (1990 – 1998)</td>
<td>DTP, Measles, OPV</td>
<td>SIBP, LIBP, KIMB, (NCL)</td>
<td>China</td>
<td>Turn-key</td>
</tr>
<tr>
<td><strong>Salk-IPV procurement (2005– now)</strong></td>
<td>Salk IPV</td>
<td>Panacea, BE, SII, Glovax</td>
<td>India, Korea</td>
<td>Bilateral agreements</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Transfer of IPV related QC testing</td>
</tr>
</tbody>
</table>
Worldwide Polio Incidence 2000 - 2009

- The risk of Vaccine associated paralytic poliomyelitis (VAPP) in countries using OPV
- In some developing countries the efficacy of tOPV was shown to be relatively low probably due to vaccine interferences
- The suboptimal response to OPV in developing countries compared to industrialized countries, may be determined by different factors related to vaccine, host and environment

Between 1,000 and 2,000 diagnosed cases per year: we may have reached a dead end!!
Main determinants guiding country decisions on polio vaccination in the pre-eradication era:

- **current polio status** (e.g. polio-free vs. endemic)

- potential for WPV importation into the country

- potential for poliovirus transmission following importation (e.g. routine EPI coverage, socio-economic status, sanitation)
Vaccine choice pre-eradication
WHO polio vaccination policy recommendations

**POLIOVIRUS TRANSMISSION POTENTIAL**

<table>
<thead>
<tr>
<th>POTENTIAL FOR IMPORTATION</th>
<th>ENDEMIC or RECURRENT OUTBREAKS</th>
<th>FULL OPV, INCLUDING BIRTH DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VERY HIGH/ HIGH</strong></td>
<td>FULL OPV or IPV/OPV/OPV**</td>
<td>FULL OPV, +/- BIRTH DOSE</td>
</tr>
<tr>
<td><strong>MODERATE</strong></td>
<td>FULL OPV or IPV/OPV sequential or IPV only</td>
<td></td>
</tr>
</tbody>
</table>

**POLIOVIRUS TRANSMISSION POTENTIAL**

- **very low/low**
  - >90-95% DPT3 in all states/provs; good personal, domestic & env. hygiene; closed sewage systems with 2o or 3o treatment.

- **moderate**
  - e.g. <90% DPT3 in all states/provs; moderate personal, domestic & env hygiene standards; incomplete secondary sewage treatment; tropical or semi-tropical climate.

- **high**
  - e.g. <90% DPT3, low personal, domestic & environmental hygiene; majority of areas with open sewage systems; tropical climate.

* very high = land border with endemic or recurrent outbreak country; high = hx of importation + high traffic; moderate = rest of world.

** in such areas, a sequential schedule can only be considered if transmission potential is VERY low & DPT3 is >95% in all states/provs.
Vaccine choice post-eradication

As soon as global polio eradication is achieved OPV will need to be stopped to avoid reintroduction of vaccine-derived polioviruses into the population.

Therefore, inactivated poliovirus vaccine (IPV) will be the only option for those countries wanting to continue to vaccinate against polio.
## Vaccine choice post-eradication

<table>
<thead>
<tr>
<th>Year</th>
<th>Potential timeline and priority activities for eventual cessation of oral poliovirus vaccine (OPV) for routine immunization</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td><strong>Interuption of wild poliovirus</strong>&lt;br&gt;Certify interruption of wild virus transmission.&lt;br&gt;Contain wild &amp; vaccine-derived polioviruses.&lt;br&gt;Develop mOPV stockpile &amp; criteria for use.&lt;br&gt;Establish national policy on IPV use.</td>
</tr>
<tr>
<td>2014</td>
<td><strong>Certification &amp; Preparation for OPV Cessation</strong>&lt;br&gt;Simultaneously stop all routine use of OPV.&lt;br&gt;Contain Sabin strain polioviruses.&lt;br&gt;Verify the absence of cVDPVs &amp; Sabin virus.&lt;br&gt;Establish national policy on IPV use.</td>
</tr>
<tr>
<td>2016</td>
<td><strong>OPV Cessation &amp; Verification</strong>&lt;br&gt;Contain Sabin strain polioviruses.&lt;br&gt;Verify the absence of cVDPVs &amp; Sabin virus.&lt;br&gt;Establish national policy on IPV use.</td>
</tr>
<tr>
<td>2020</td>
<td><strong>‘Post OPV’ Era</strong>&lt;br&gt;Maintain surveillance.&lt;br&gt;Maintain stockpile.&lt;br&gt;Verify containment.&lt;br&gt;Establish national policy on IPV use.</td>
</tr>
</tbody>
</table>

### Timeline

- **Years after last circulating wild poliovirus**
  - Years: 0, 1, 2, 3, 4, 5, 6, 7, 8

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**http://www.polioeradication.org**

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*Developing Countries Vaccine Manufacturers Network (DCVMN), September 15-16, 2010 in Hyderabad, India.*
The potential exists for a significant improvement in the supply and manufacturing economics of IPV vaccine for low-income countries

- Tracking key development milestones and supporting research in technologies critical to reducing the manufacturing cost
- Develop new or alternative sources of IPV capacity (e.g. S-IPV) or and use of adjuvants
- Keep supply and demand balanced, by keeping manufacturers up to date. Engagement of countries and donors as GAVI is needed.
- Co-funding the investments in R&D or facilities or ensuring long/term demand for the vaccine may be needed.
Vaccine choice post-eradication

IPV is currently considered to be too expensive for use for routine immunization in developing countries, strategies to make IPV more affordable are being evaluated, including:

- Intradermal delivery (IDD) of reduced volumes of vaccine per dose.
- Use of adjuvants to allow a reduced IPV antigen content per dose.
- Reducing the number of doses per IPV immunization schedule.
- Use of IPV in combination vaccine formulations.
- IPVs based on Sabin (attenuated) strains to reduce biosafety concerns and to facilitate production in countries where vaccine manufacture is less expensive.
WHO's Commitment

- World Health Assembly (WHA) directed WHO to develop ‘safer processes for production of inactivated poliovirus vaccine and affordable strategies for its use’ for developing countries (May 2008, Resolution 61.1)

- Bill and Melinda Gates Foundation (BMGF) also requested WHO to provide ‘sIPV global access strategy’, including strategy to ensure ‘the vaccine will be made available to the public sector of developing countries in sufficient quantities and at affordable price’
WHO's Commitment

- WHO re-emphasized its commitments to developing ‘affordable IPV option and policy for low- and middle-income countries’ in its 2009 ‘program of work’ report, including
  - S-IPV development
  - Intradermal IPV
  - Adjuvant
  - Alternate seed strain
  - Alternative schedule (1 or 2 doses)
WHO's Commitment

- Consultation for the revision of the current Technical Report Series (TRS) to be initiated in 2011

- Working group to be convened when the WHO Sabin-IPV development project is more advanced and data is available:
  - Phase I/II trial completed and safety and immunogenicity demonstrated through preliminary data
  - Antigenicity and immunogenicity assay standardized (method and reagents/references)
  - Optimization of the production method more advanced (inactivation and adjuvant)
  - “sabin-like” master seed stock in place
  - Post-eradication biosafety requirements fully endorsed
  - Estimated timeframe: Q4, 2012

- Drafting group to be established
  - Revised TRS to be drafted
  - Estimated timeframe: Q2, 2013

- Expert Committee on Biological Standardization (ECBS).
  - Revised TRS to be endorsed and published
  - Estimated timeframe: Q4, 2013

Developing Countries Vaccine Manufacturers Network (DCVMN), September 15-16, 2010 in Hyderabad, India.
Developing a S-IPV vaccine at the NVI

A MOU between NVI and WHO was signed in Q4 2008

Developing Countries Vaccine Manufacturers Network (DCVMN), September 15-16, 2010 in Hyderabad, India.
Sabin-IPV vaccine project 2008 - now

- Sabin-IPV based on NVI Salk-IPV Vero/ micocarrier technology
- Production of Master/ Working seedlot
- Preparation of clinical lots and process fine-tuning/ optimization
- (Pre)clinical and phase I clinical studies
- Technology Transfer to potential partners
Sabin-IPV vaccine project
2008 - now

Source material:
- Type 1: WHO / Behringwerke 1976 SO+1
- Type 2: WHO / Behringwerke 1976 SO+1
- Type 3: Institut Mérieux 1963 (457-Pfizer) RSO1

Master Seed Lots (3 types): 10-L scale

Working Seed Lots (3 types): 350-L scale
Sabin-IPV vaccine project
2008 – now
Master (3x) & Working (3x) Seedlots prepared
Sabin-IPV vaccine project
2008 – now
6 lots monovalent pools prepared under GMP

Upstream processing
Vero cell
Media
Virus

Downstream processing
Monovalent pool

Inactivation
Process updated
where appropriate:
Clarification modernized

Developing Countries Vaccine Manufacturers Network (DCVMN), September 15-16, 2010 in Hyderabad, India.
Sabin-IPV vaccine project
2008 - now

- Pre-clinical lots (safety) : started, May 2010
- Phase I clinical lots : planned, Q1 2011
Sabin-IPV vaccine project  
2008 – now

Phase I Clinical trial age de-escalation

<table>
<thead>
<tr>
<th>Age group</th>
<th>Arm</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult (19-49 yrs)</td>
<td>Normal (High dose)</td>
<td>0 2 4 5 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50</td>
</tr>
<tr>
<td></td>
<td>Adjuvant (High dose)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15/arm</td>
<td></td>
</tr>
<tr>
<td>Toddler (4-10 yrs)</td>
<td>Normal (High dose)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjuvant (High dose)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15/arm</td>
<td></td>
</tr>
<tr>
<td>Infants (2 mos)</td>
<td>Normal sIPV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjuvant sIPV (low)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20/arm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal sIPV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjuvant sIPV (Middle)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal sIPV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjuvant sIPV (High)</td>
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<tr>
<td></td>
<td>WPV</td>
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<tr>
<td></td>
<td>DSMB</td>
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</tbody>
</table>

**Suggested Phase I Approach**

- IPV
- Blood collection
Sabin-IPV vaccine formulation considerations:

- Neutralizing antibody titre should be equal or higher than that induced by the international (Salk-IPV) reference

<table>
<thead>
<tr>
<th></th>
<th>Plain formulation (DU / single human dose)</th>
<th>Al(OH)_3 formulation (DU / single human dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Target</td>
</tr>
<tr>
<td>Type 1</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Type 2</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>Type 3</td>
<td>64</td>
<td>32</td>
</tr>
</tbody>
</table>

For reference: plain Salk-IPV formulation is (type 1 – 2 – 3): 40 – 8 – 32 DU/shd
Technology Transfer of Sabin-IPV technology

Workshop on ‘Sabin IPV: Challenges and Benefits’
28-30 June 2010

Developing Countries Vaccine Manufacturers Network (DCVMN), September 15-16, 2010 in Hyderabad, India.
Technology Transfer of Sabin-IPV technology

Polio Eradication Initiative
Call for Expressions of Interest (EoI)
Developing Sabin-Inactivated Polio Vaccine (sIPV)

12 Interested Parties

4 most potential partners will be selected by WHO, guided by an ad-hoc selection committee, and requested to submit additional documents

Q2 2011 TT will start to the first 2 partners

Time schedule
WHO/NVI Sabin-IPV Workshop on ‘Sabin IPV: Challenges and Benefits’
28-30 June 2010
Bilthoven, the Netherlands
Summary

• A renewed RIVM/NVI public entity will continue to serve as R&D vaccinology resource institute for DCVMN

• Technology Transfer programs with WHO on polio will be carried out.

• OPV has been the vaccine of choice for the Global Polio Eradication Initiative; it has eradicated type 2 and eliminated type 1 and type 3 polio in 3 of the 6 WHO regions. But IPV vaccine may be needed to complete the work……

• A substantial programme of work is ongoing to better understand the role IPV could play in both the pre- and post-eradication eras.
Summary

• As soon as Global Polio Eradication is achieved vaccination with OPV should stop to avoid reintroduction of vaccine-derived polioviruses into the population. IPV will be the only option for those countries wanting to continue to vaccinate against polio.

• Commitment from DCVM´s is needed to significantly improve the supply and manufacturing economics of IPV vaccine

• NVI will start the Transfer of Sabin-IPV technology to the first two potential partners in Q2 2011
Questions?
Countries using only IPV
Countries using sequential schedules of IPV and OPV
Countries expected to use sequential schedules of IPV and OPV
Countries using only OPV

Developing Countries Vaccine Manufacturers Network (DCVMN) Symposium
15-16, 2010 in Hyderabad, India.
Vaccine choice pre-eradication
IPV Combination in Routine Programs, 2008

Developing Countries Vaccine Manufacturers Network (DCVMN) 15-16, 2010 in Hyderabad, India.
Vaccine choice post-eradication

Exhibit A: Potential future IPV-containing hexavalent vaccine manufacturers (sample)

Current IPV-containing combination vaccine suppliers
- GSK (BE)
- Sanofi-Pasteur (FR/US)

Other combination vaccine suppliers
- Current pentavalent (DTwP-HepB-Hib) manufacturers
  - Crucell (NL)
  - Panacea Biotech (IN)
  - Shantha Biotec (IN)
  - Serum Institute of India (IN)
- Manufacturers with pentavalents in development
  - Bharat Biotech (IN)
  - Biological E (IN)

Other IPV vaccine suppliers
- Current manufacturers
  - Netherlands Vaccine Institute (NL)
  - Statens Serum Institute (DE)
- Manufacturers with IPV in development
  - Kunming Institute (CN)
  - Takoda (JP)