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

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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

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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.

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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

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Introduction to NVI

Letter of Ministry of Health, Welfare and Sport, dated **January 14, 2010***. Attn: The President of the House of Representatives of the States General:*

'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**'.

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Introduction to NVI

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

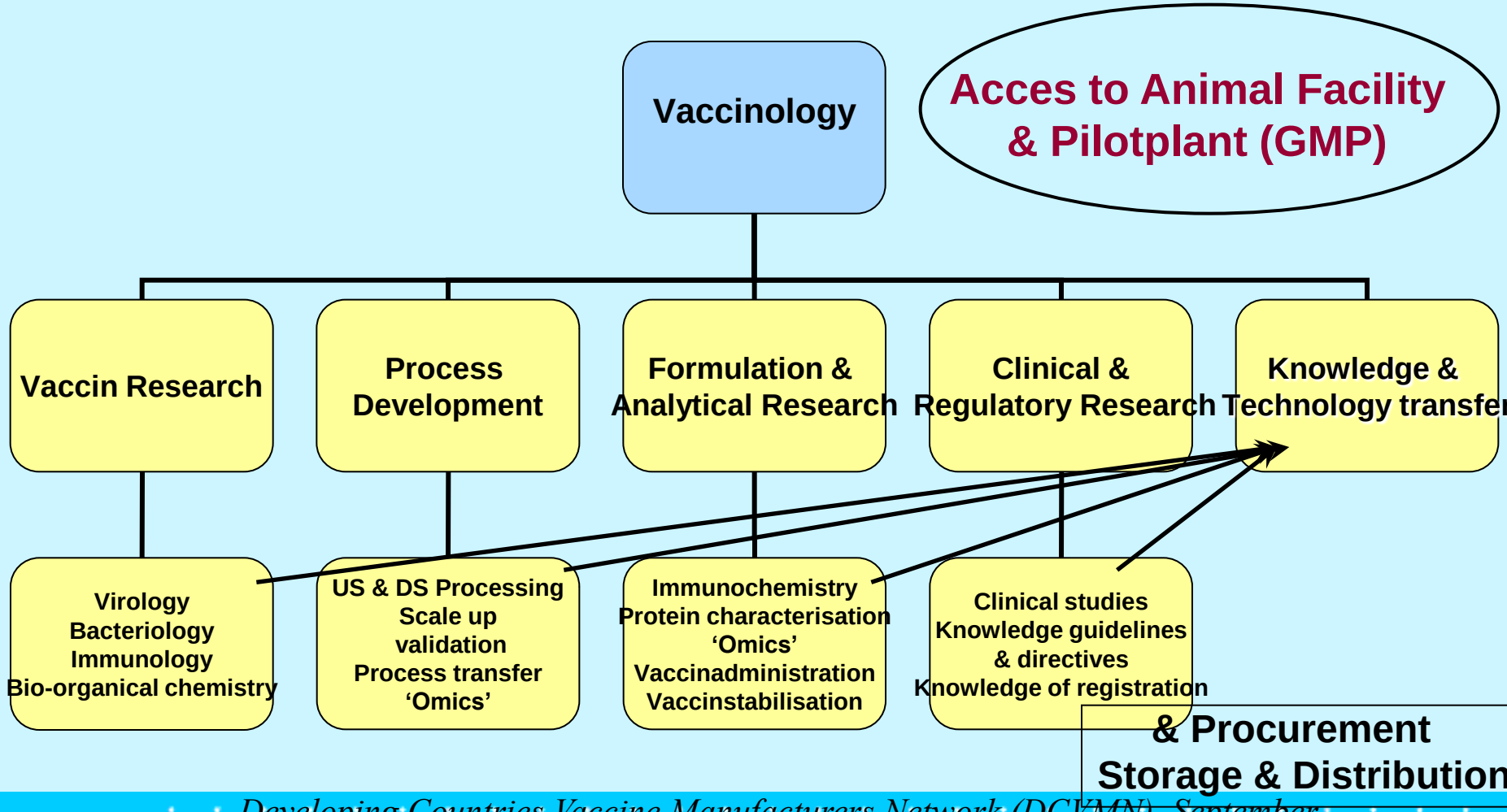
Introduction to NVI

c) Public vaccine functions will be integrated within a reorganized RIVM

´…….*integrated implementation within a single organization will optimally strengthen the public tasks´*

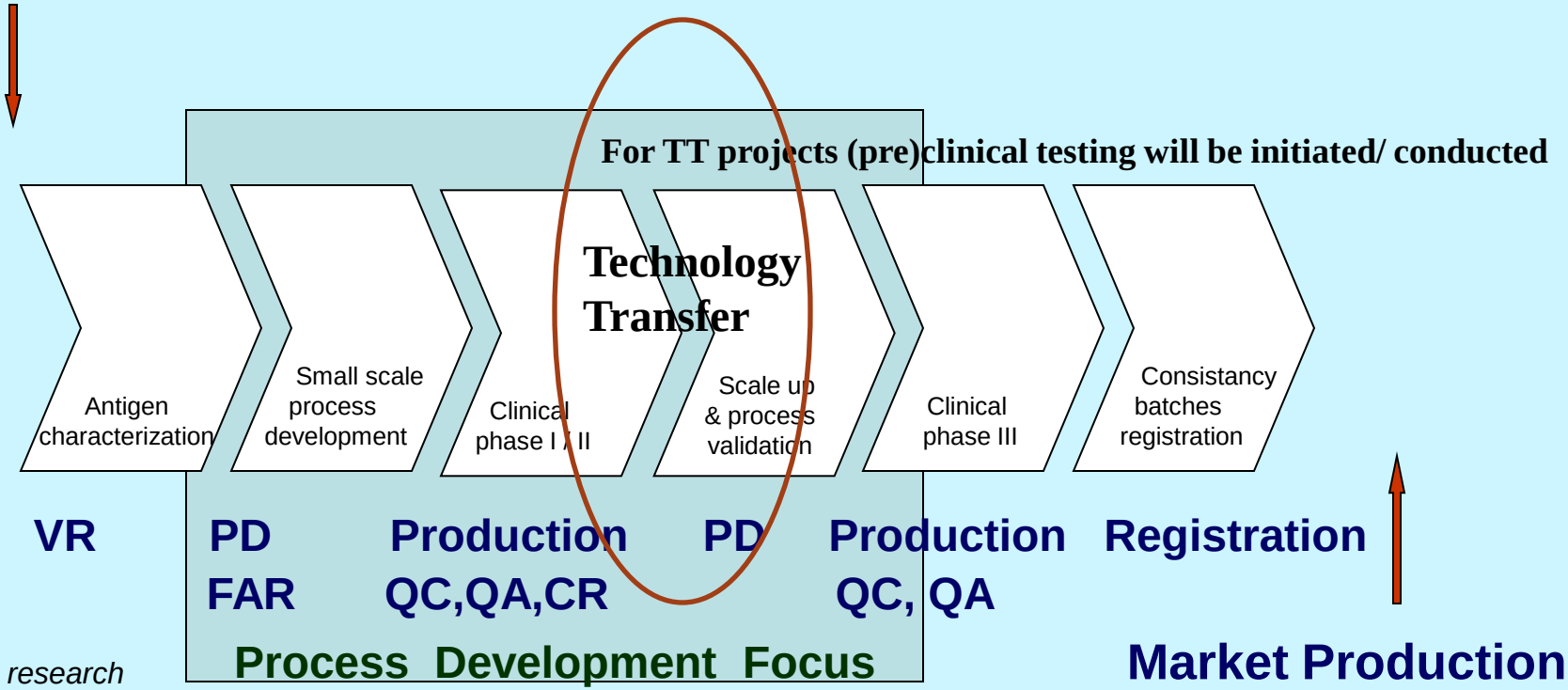
Integration will start January 2011 and be functional by January 2012

Public Vaccine functions integrated in RIVM departments and expertises



Introduction to NVI

New Vaccine Idea



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

Introduction to NVI

Salk-IPV production will be privatized

- Existing supply agreements will be honored

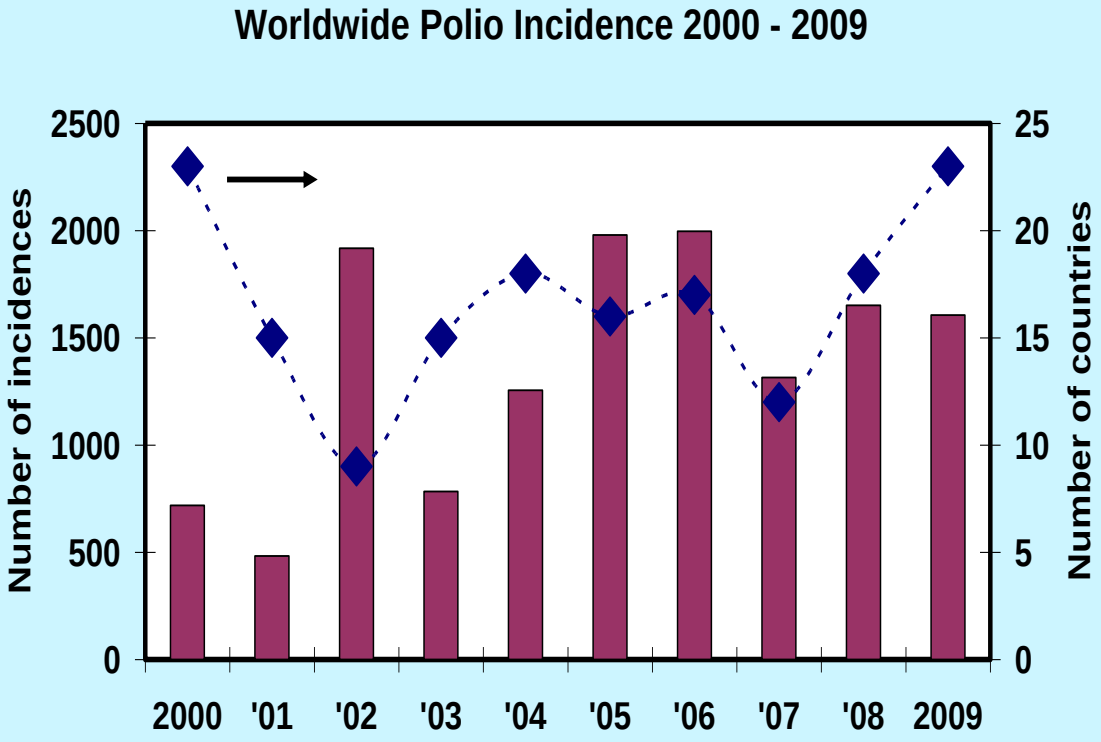
Sabin-IPV project will remain in the public domain

- Transfer of Sabin-IPV technology to potential partners will start in 2011

Polio related Technology Transfer and training since 1970

Project	Vaccine(s)	Recipient	Country	Approach
Micro-carrier technology (1970-1980)	Viral vaccines	**Sanofi, GSK, Sclavo (Novartis)…**	Several	Turn-key
WHO Course on Laboratory methods for titration of Live Virus Vaccines 1990	OPV en Measles		Egypt	
Training Course on Vaccine Potency Testing and Polio Diagnostic Procedures 1990-1994	OPV		China, India, Sri Lanka and Brazil.	
China Vaccine Project, World Bank (1990 – 1998)	DTP, Measles, OPV	SIBP, LIBP, KIMB, (NCL)	China	Turn-key
Salk-IPV procurement (2005– now)	Salk IPV	Panacea, BE, SII, Glovax	India, Korea	Bilateral agreements Transfer of IPV related QC testing

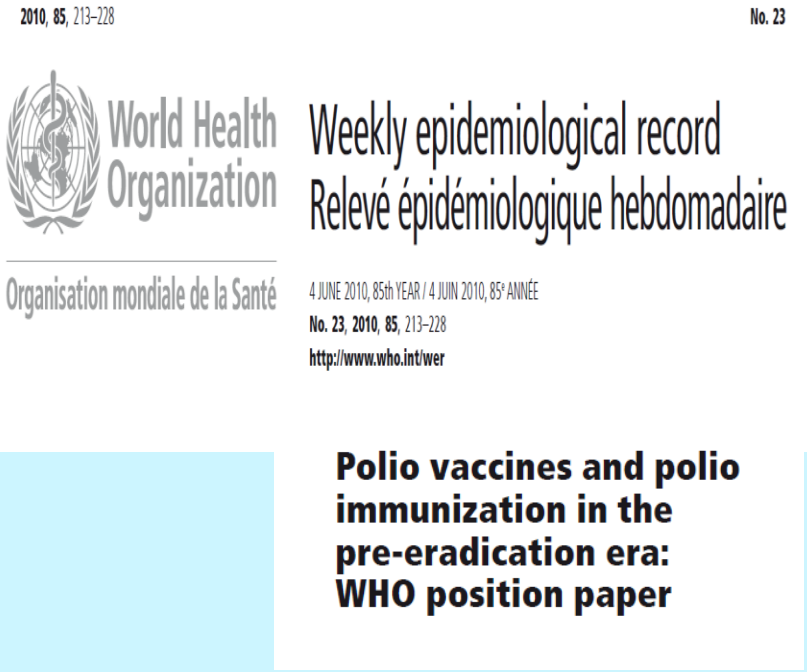
Vaccine choice pre-eradication



- 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!!

Vaccine choice pre-eradication


2010, 85, 213–228 No. 23

World Health Organization

Organisation mondiale de la Santé

Weekly epidemiological record

Relevé épidémiologique hebdomadaire

4 JUNE 2010, 85th YEAR / 4 JUIN 2010, 85e ANNÉE

No. 23, 2010, 85, 213–228

http://www.who.int/wer

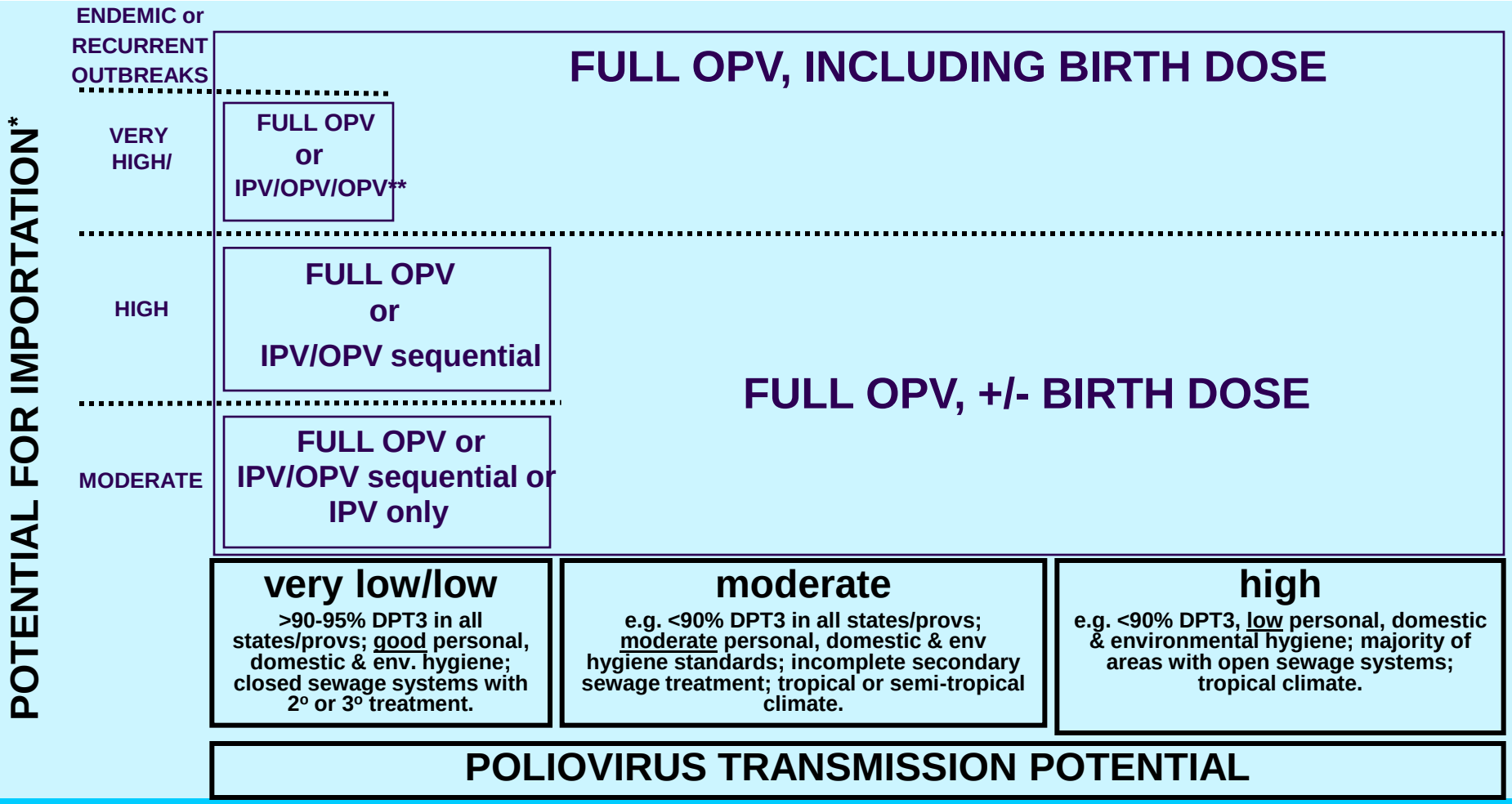
Polio vaccines and polio immunization in the pre-eradication era: WHO position paper

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



* 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.

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Vaccine choice post-eradication

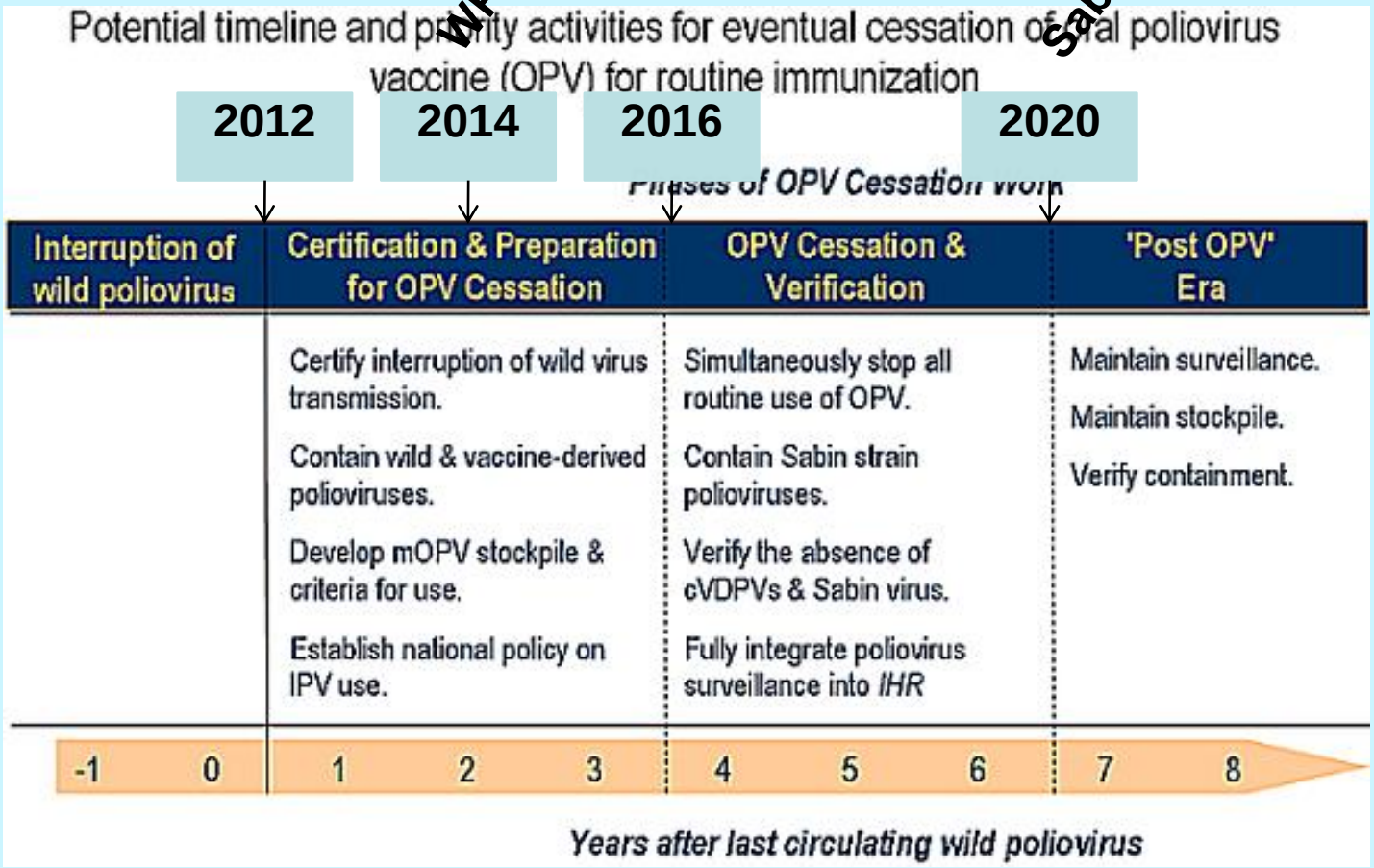
As soon as global polio eradication is achieved OPV will need to be stopped to avoid reintroduction of vaccine-derived polioviruses into the population.

Therefore, inactivated poliovirus vaccine (IPV) will be the only option for those countries wanting to continue to vaccinate against polio.

Vaccine choice post-eradication

WPV containment

Sabin containment



http://www.polioeradication.org

Vaccine choice post-eradication

The supply landscape and economics of IPV-containing combination vaccines: Key findings

Commissioned by the Bill & Melinda Gates Foundation

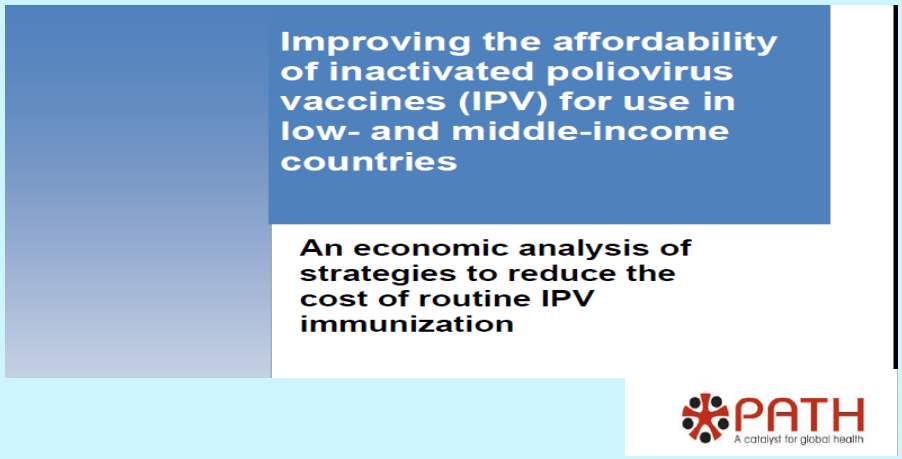
Prepared by Oliver Wyman, www.oliverwyman.com

May 2010

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



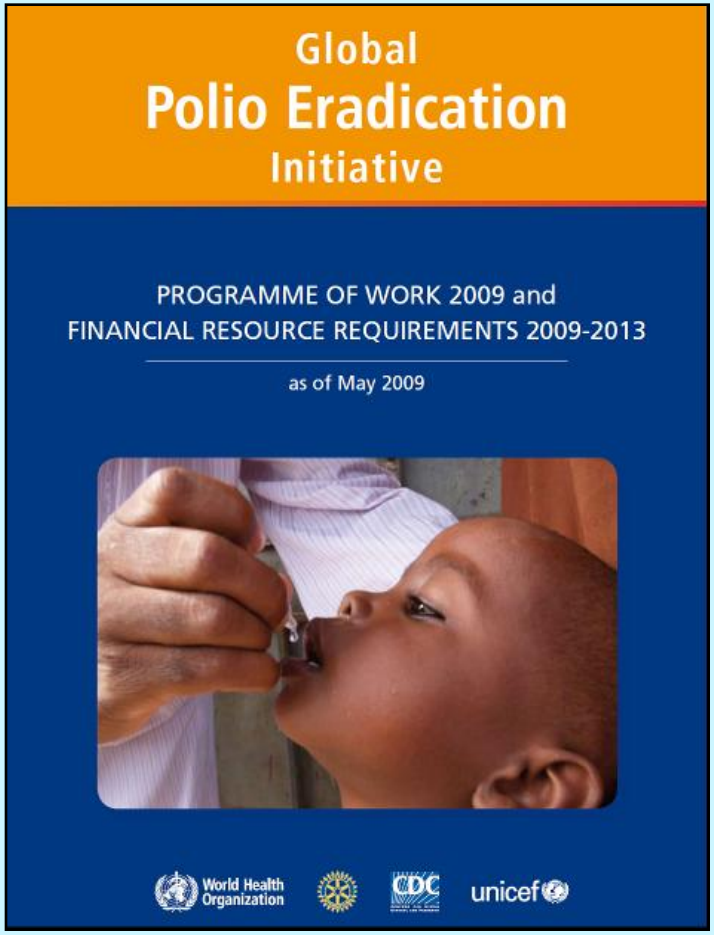
IPV is currently considered to be too expensive for use for routine immunization in developing countries, strategies to make IPV more affordable are being evaluated, including:

- **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**

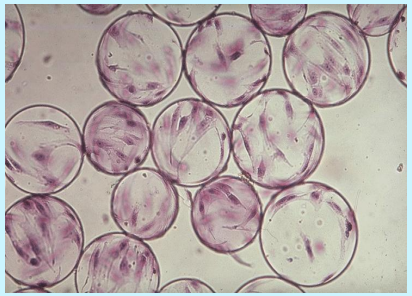
- Drafting group to be established
  - Revised TRS to be drafted
  - Estimated timeframe: **Q2, 2013**

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

Developing a S-IPV vaccine at the NVI

A MOU between NVI and WHO was signed in Q4 2008

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

↓

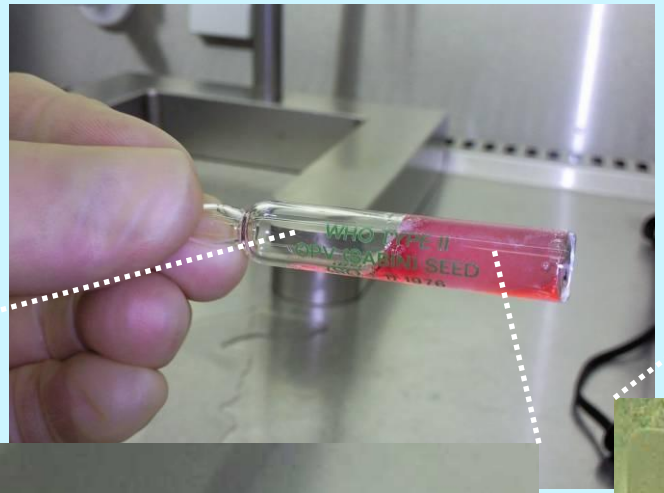
Master Seed Lots (3 types) : 10-L scale

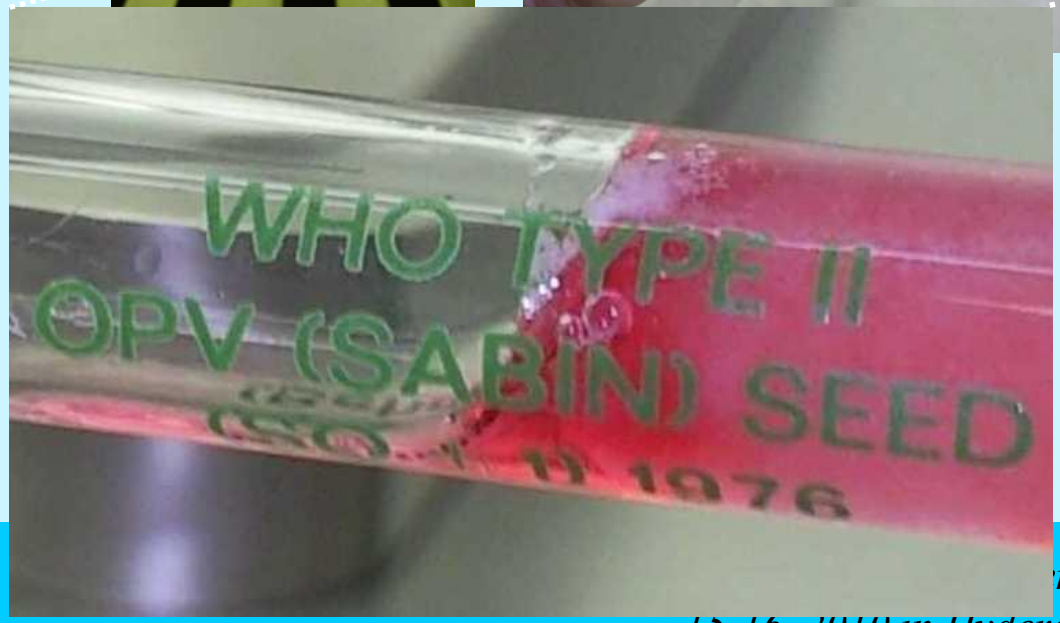
↓

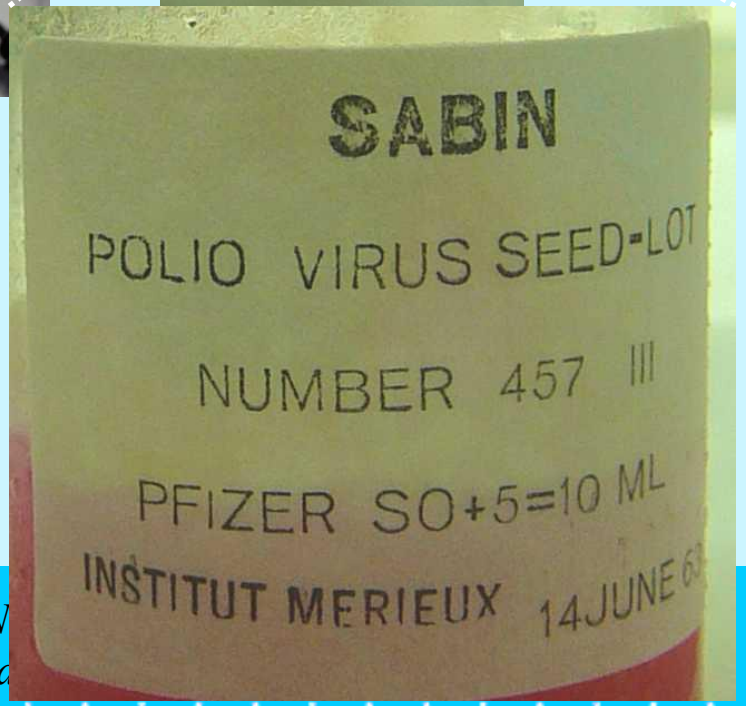
Working Seed Lots (3 types): 350-L scale

Sabin-IPV vaccine project 2008 – now

Master (3x) & Working (3x) Seedlots prepared







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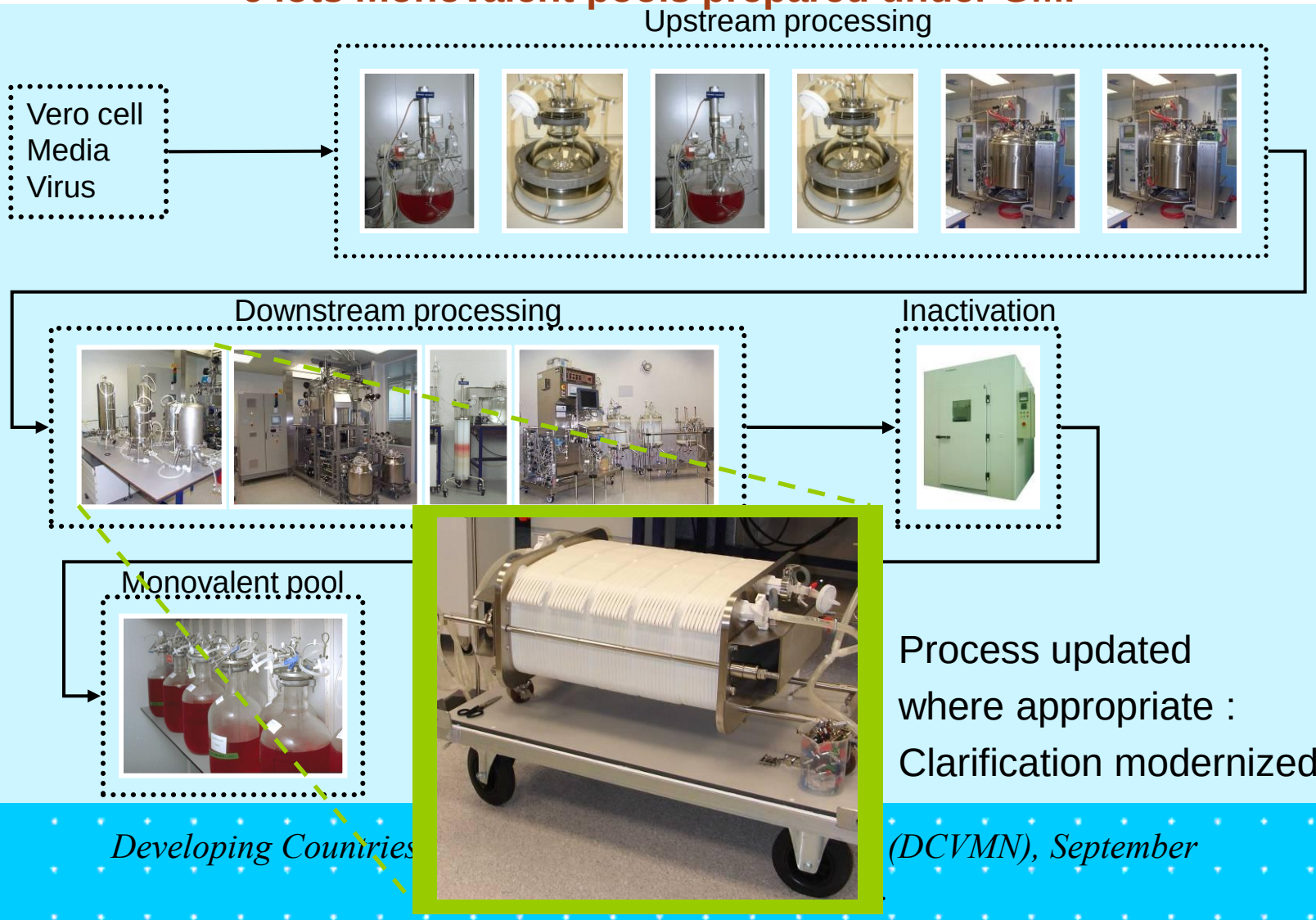
15-16, 2010 in Hyderabad

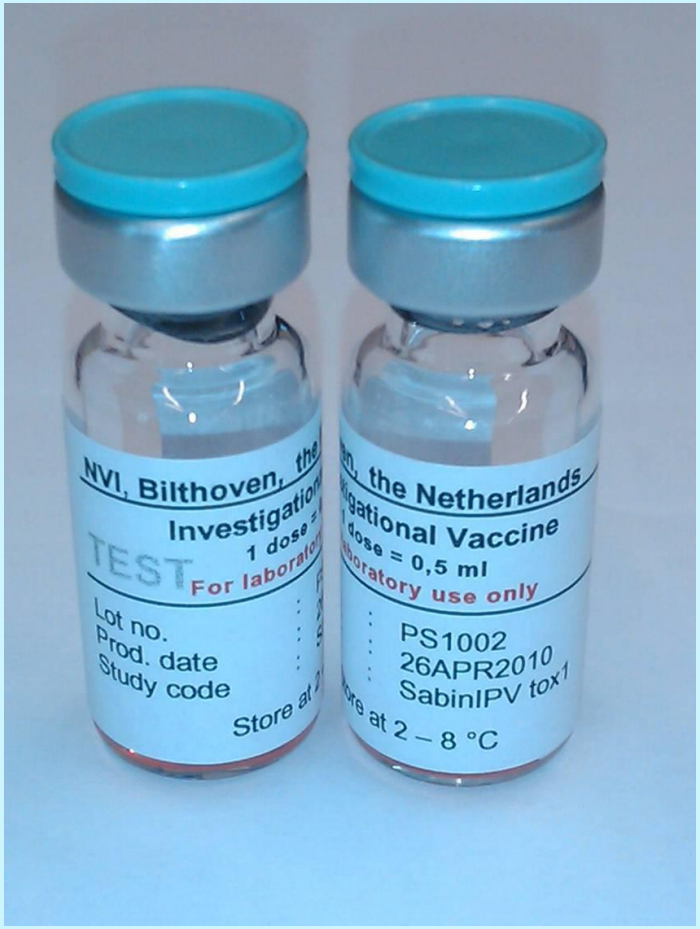
Sabin-IPV vaccine project 2008 – now

6 lots monovalent pools prepared under GMP



Process updated where appropriate :
Clarification modernized

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

Suggested Phase I Approach

★ IPV
☆ Blood collection

Age group	Arm		Weeks 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50
Adult (19-49 yrs) 15/arm	▪ Normal (High dose) ▪ Adjuvant (High dose) – 15/arm	Administration Follow-up	★ ☆ – ☆
		DSMB	–
Toddler (4-10 yrs) 15/arm	▪ Normal (High dose) ▪ Adjuvant (High dose)	Administration Follow-up	★ ☆ – ☆
		DSMB	–
Infants (2 mos) 20/arm	▪ Normal sIPV Adjuvant sIPV (low)	Administration Follow-up	★ ★ ★ ☆ – – – – – – – – – – ☆
	▪ Normal sIPV Adjuvant sIPV (Middle)	Administration Follow-up	★ ★ ★ ☆ – – – – – – – – – – ☆
	▪ Normal sIPV Adjuvant sIPV (High)	Administration Follow-up	★ ★ ★ ☆ – – – – – – – – – – ☆
	▪ WIPV	Administration Follow-up	★ ★ ★ ☆ – – – – – – – – – – ☆
		DSMB	– – –

Sabin-IPV vaccine project 2008 – now

formulation for (pre)-clinical studies

Sabin-IPV vaccine formulation considerations:

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

	Plain formulation (DU / single human dose)			$Al(OH)_3$ formulation (DU / single human dose)		
	High	Target	Low	High	Target	Low
Type 1	20	10	5	10	5	2.5
Type 2	32	16	8	16	8	4
Type 3	64	32	16	32	16	8

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

Technology Transfer of Sabin-IPV technology

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

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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.

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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

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Questions?

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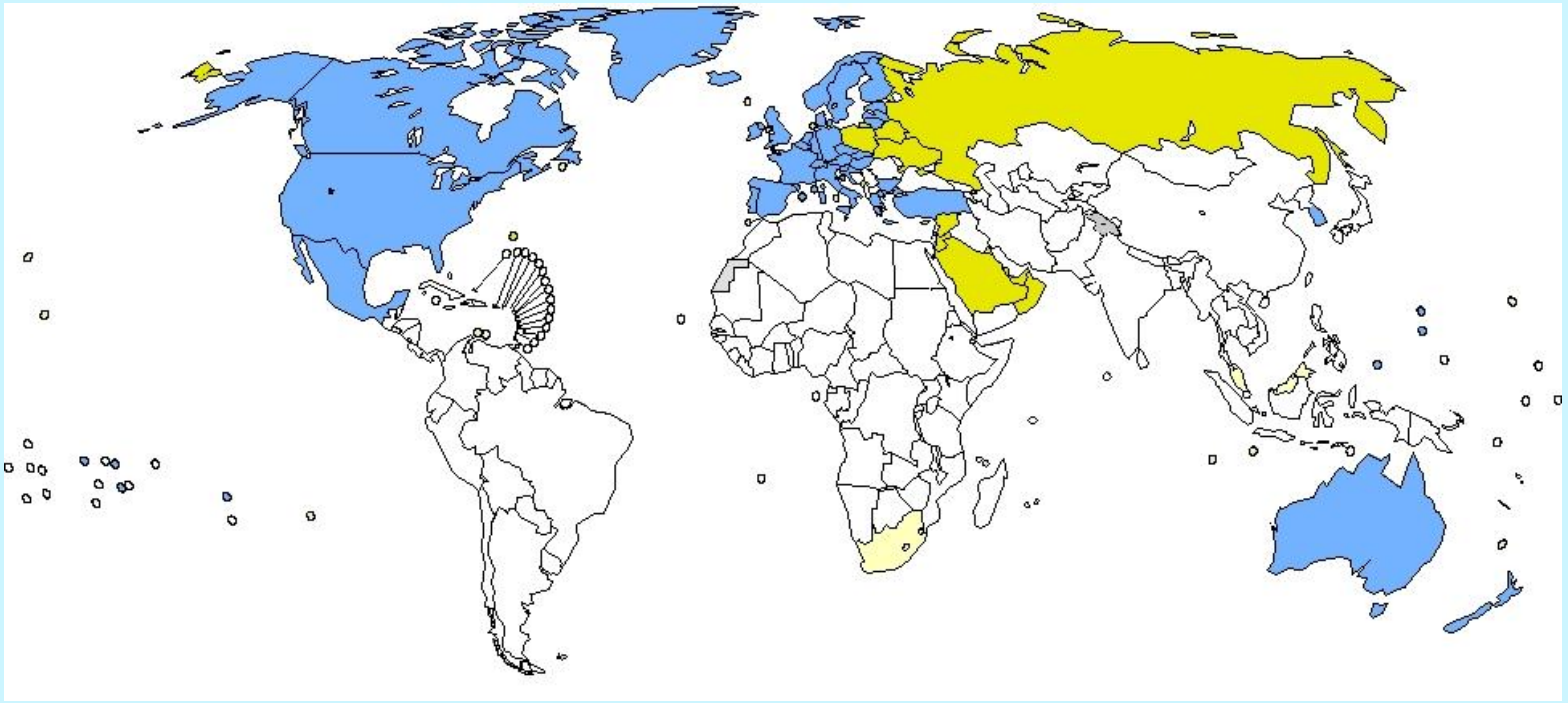
Vaccine choice pre-eradication

Polio Schedules in Routine Programs, 2008



Countries using only IPV

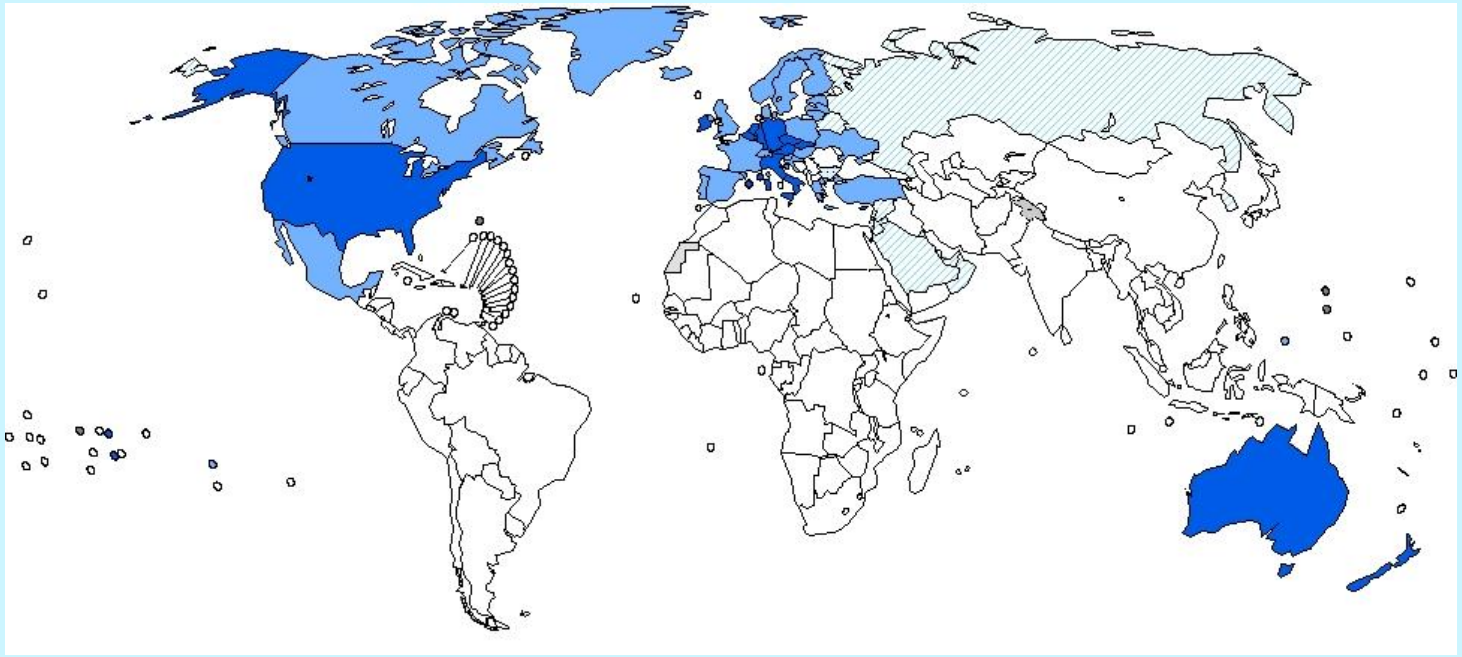
Countries using sequential schedules of IPV and OPV

Countries expected to use sequential schedules of IPV and OPV

Countries using only OPV

Vaccine choice pre-eradication

IPV Combination in Routine Programs, 2008



- Standalone IPV
- IPV - tetra combo
- IPV - penta combo
- IPV - hexa combo
- Unknown
- Not applicable

Vaccine choice post-eradication

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

Current IPV-containing combination vaccine suppliers	Other combination vaccine suppliers	Other IPV vaccine suppliers
• GSK (BE) • Sanofi-Pasteur (FR/US)	• Current pentavalent (DTwP-HepB-Hib) manufacturers – Crucell (NL) – Panacea Biotech (IN) – Shantha Biotech (IN) – Serum Institute of India (IN) • Manufacturers with pentavalents in development – Bharat Biotech (IN) – BiologicalE (IN)	• Current manufacturers – Netherlands Vaccine Institute (NL) – Staten Serum Institute (DE) • Manufacturers with IPV in development – Kunming Institute (CN) – Takeda (JP)