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

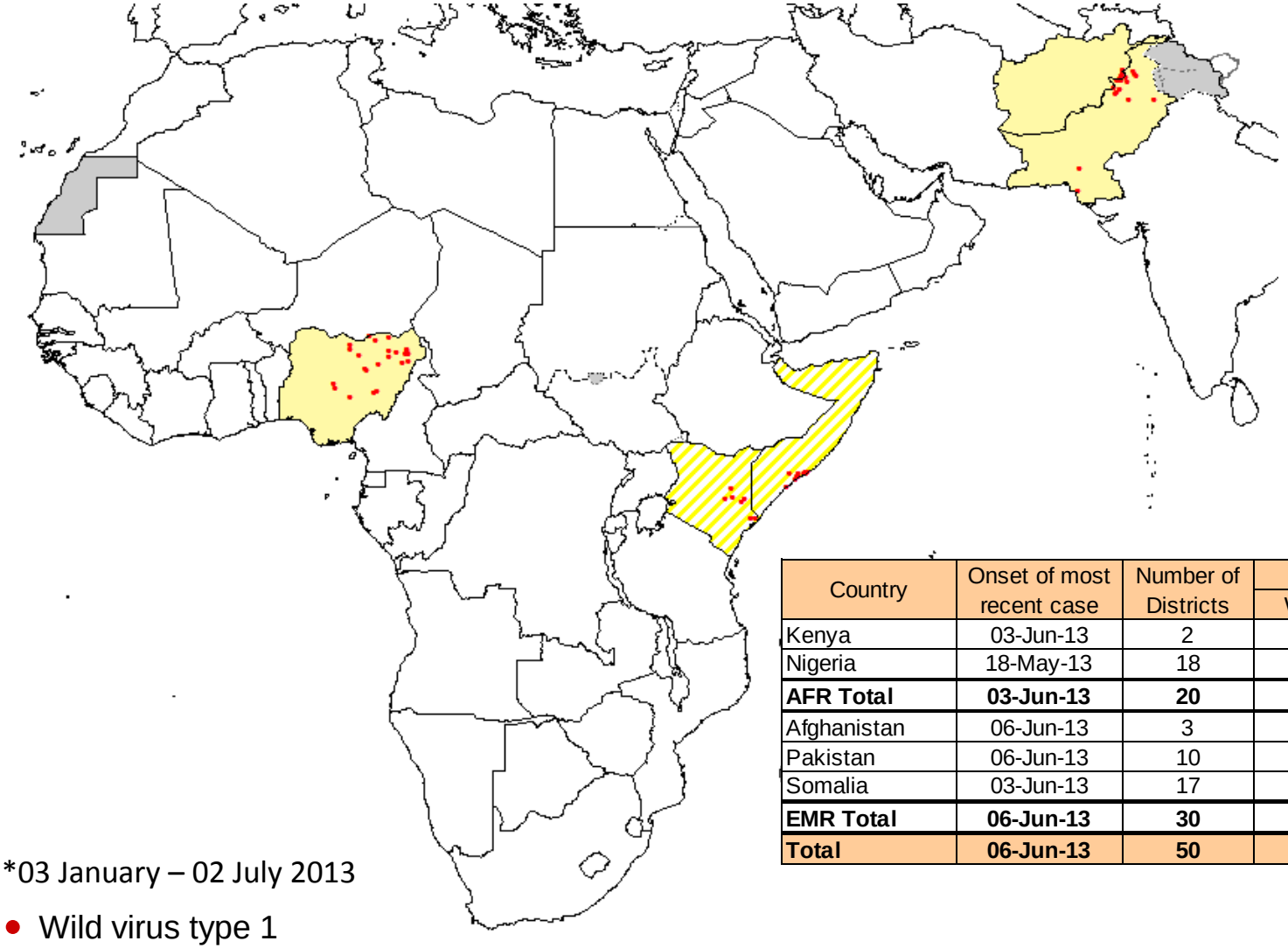
Presentation overview

- 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

Wild Poliovirus, Previous 6 Months*



Country	Onset of most recent case	Number of Districts	Virus Type		TOTAL WPV
			W1	W3	
Kenya	03-Jun-13	2	7		7
Nigeria	18-May-13	18	26		26
AFR Total	**03-Jun-13**	**20**	**33**		**33**
Afghanistan	06-Jun-13	3	3		3
Pakistan	06-Jun-13	10	18		18
Somalia	03-Jun-13	17	41		41
EMR Total	**06-Jun-13**	**30**	**62**		**62**
Total	**06-Jun-13**	**50**	**95**	**0**	**95**

*03 January – 02 July 2013

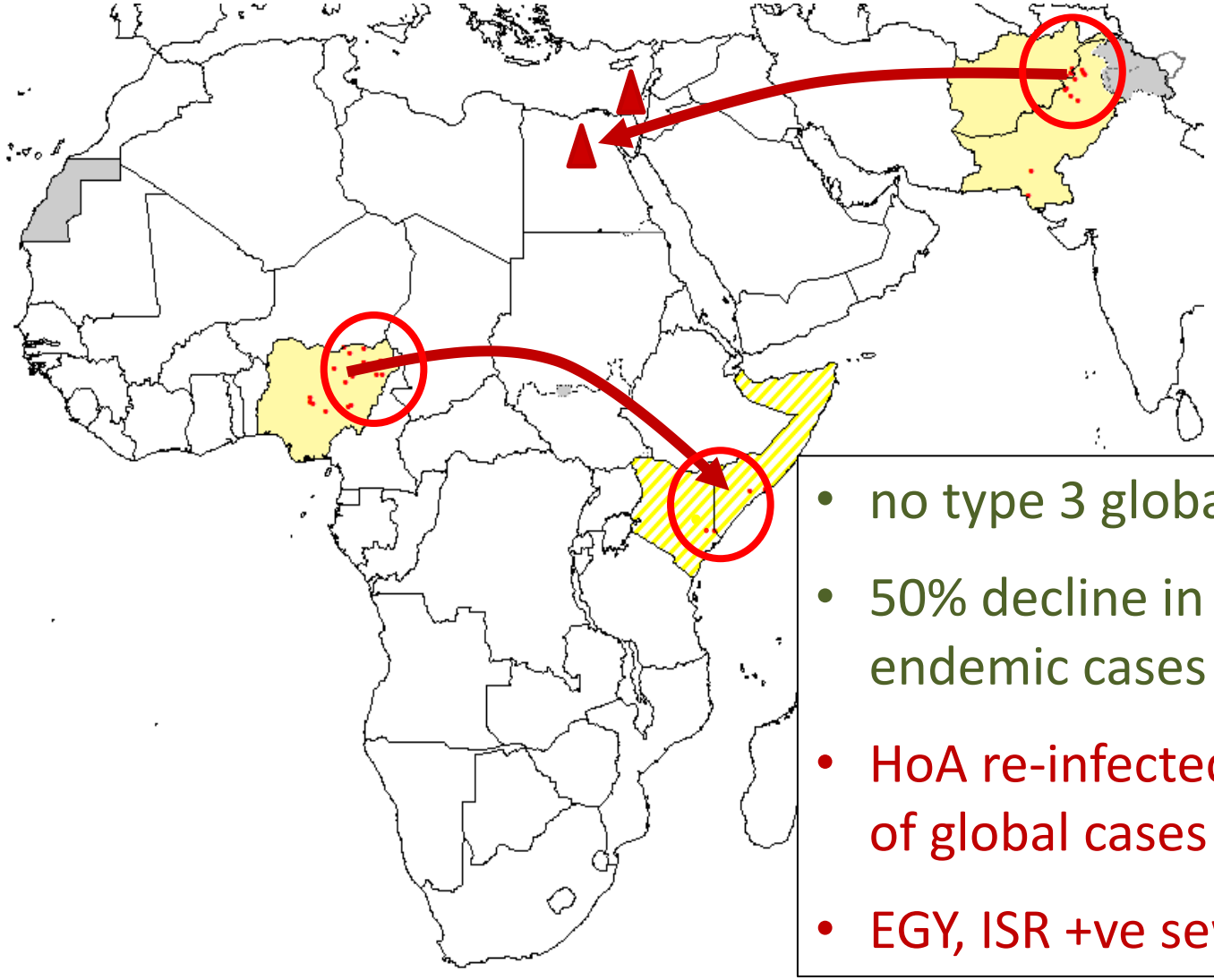
- Wild virus type 1

Endemic country

Country with WPV case in previous 6 months

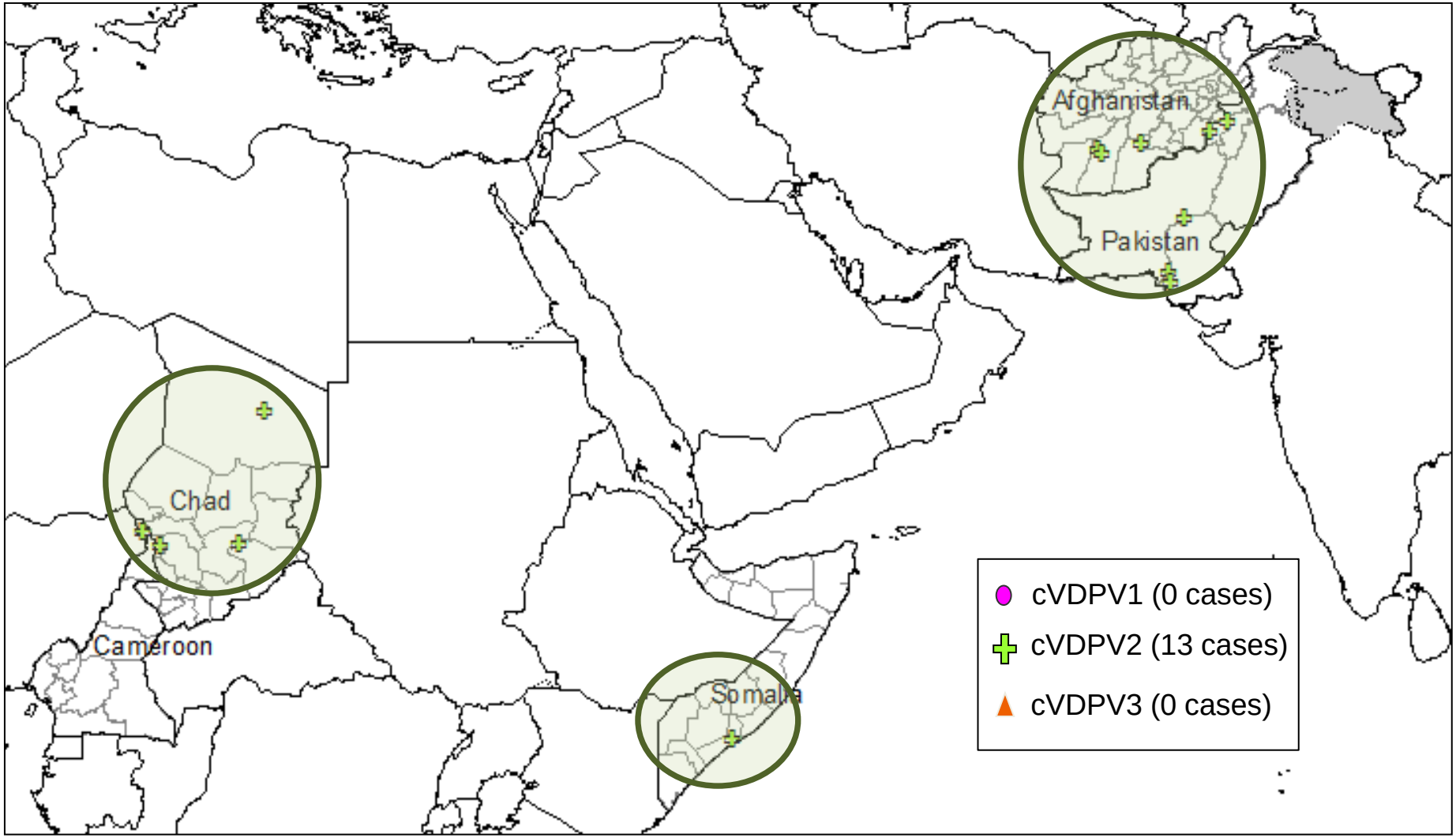
Data in WHO HQ as of 02 July 2013

Polio Paralyzed Children, last 6 months

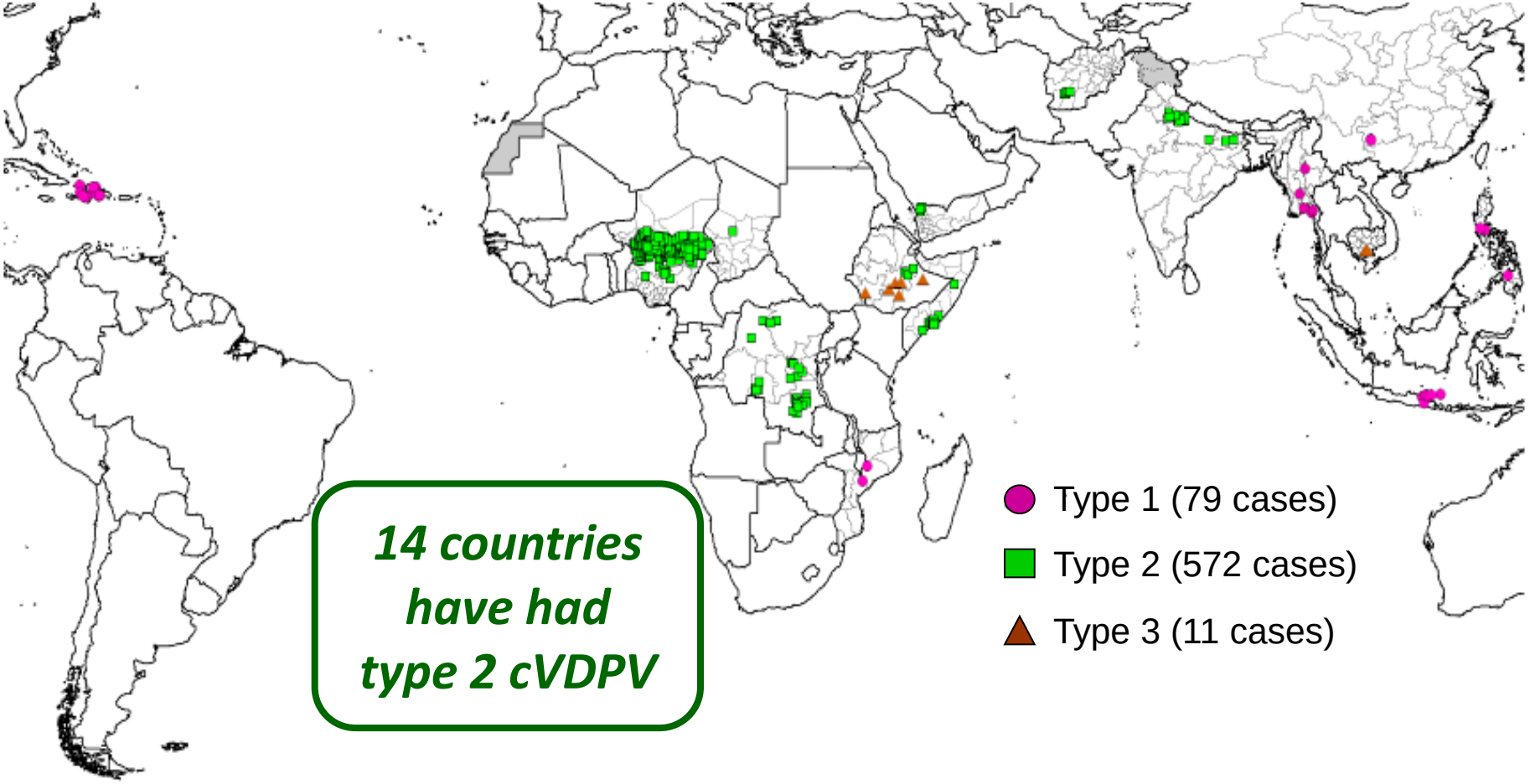


- no type 3 globally
- 50% decline in endemic cases vs 2012
- HoA re-infected & 50% of global cases
- EGY, ISR +ve sewage

cVDPV active outbreaks, last 6 months



The highest risk: cVDPV outbreaks, 2000-2013



Polio Eradication & Endgame Strategic Plan 2013-2018

Background

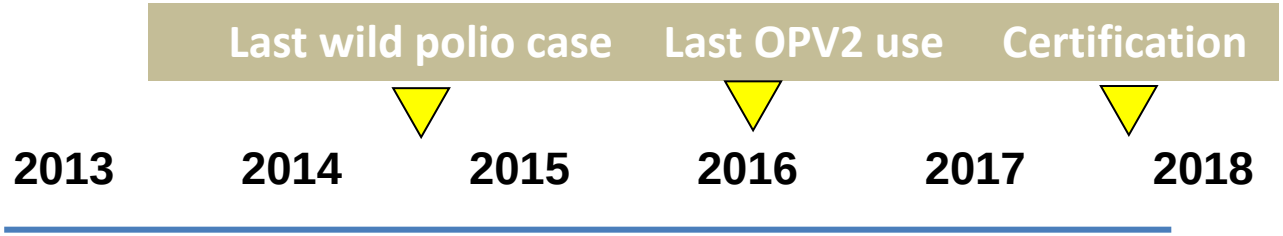
In May 2012, the WHA declared the completion of poliovirus eradication to be a programmatic emergency.

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	Wild virus interruption	Outbreak response (esp. cVDPVs)
RI strengthening & OPV withdrawal	RI strengthening & OPV2 pre-requisites	Introduce IPV; OPV2 withdrawal
Containment & certification	Finalize long-term containment plans	Complete containment & certification globally
Legacy Planning	Consultation & strategic plan	Initiate implementation of legacy plan

What is the new endgame approach to immunization policy?

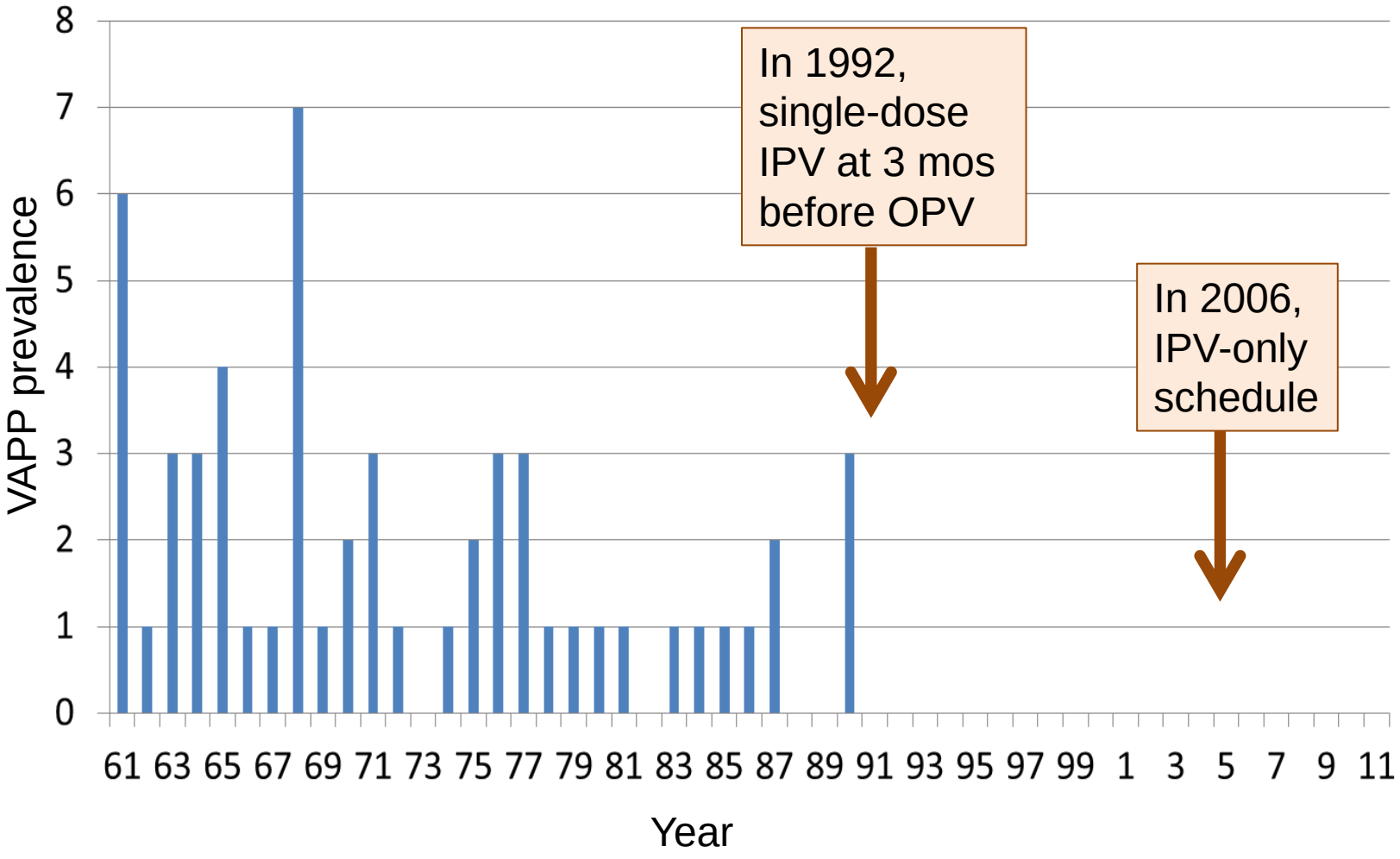
- *Sequential* cessation of oral Sabin vaccine strains, starting with Sabin type 2.
- *Replacing* tOPV with bOPV in a synchronized manner globally as the first step in OPV cessation.
- *Mitigating risk* by including at least one dose of IPV in the routine EPI in addition to OPV (starting ≥6 months before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

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)*

2013, 88, 1–16 No. 1

World Health Organization

Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

4 JANUARY 2013, 88th YEAR / 4 JANVIER 2013, 88e ANNÉE
No. 1, 2013, 88, 1–16
http://www.who.int/wer

Contents

Sommaire

Meeting of the Strategic Advisory Group of Experts on immunization, November 2012 – conclusions and recommendations

The Strategic Advisory Group of Experts (SAGE) on immunization[1] met on 6–8 November 2012 in Geneva, Switzerland. This report provides a summary of the discussions, conclusions and recommendations.[2]

Réunion du Groupe stratégique consultatif d'experts sur la vaccination, novembre 2012 – conclusions et recommandations

Le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination[1] s'est réuni du 6 au 8 novembre 2012 à Genève (Suisse). Le présent rapport donne un résumé des discussions, ainsi que les conclusions et recommandations auxquelles il est parvenu.[2]

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

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.

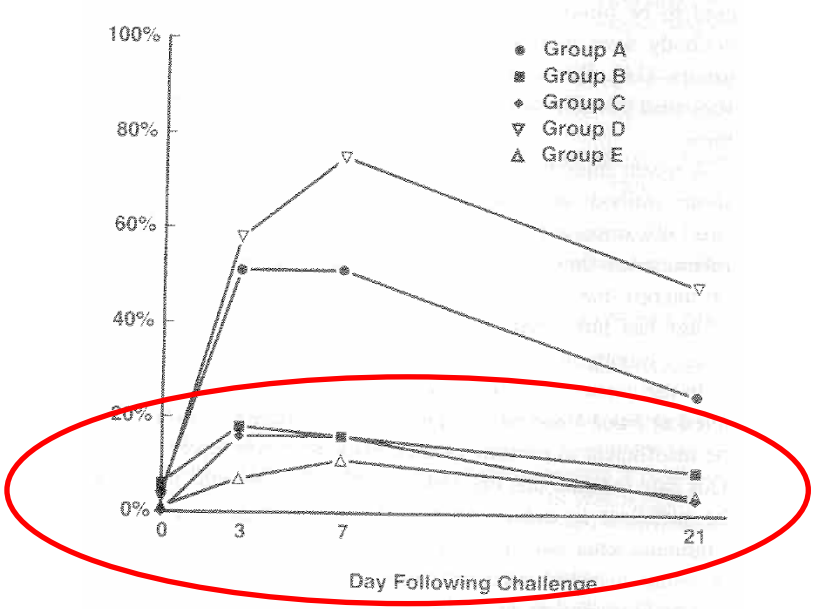


Figure 5. Proportion of subjects who shed polioviruses (any type) on day of challenge and 3, 7, and 21 days after challenge, by study group. Group A, 2 IPV doses, 1 OPV dose; group B, 2 IPV doses, 2 OPV doses; group C, 2 IPV doses, 3 OPV doses; group D, 3 IPV doses; group E, 3 OPV doses (see table 1).

Early vs. later IPV administration

			seroconversion
Author year (ref)	Country	Schedule	Type 2
Intramuscular administration of 1 dose			
McBean 88 [45]	US	2 mo	35%
Simasathien 94 [46]	Thailand	2 mo	39%
Resik 10 [40]	Cuba	6 wk	36%
Mohammed 10 [47]	Oman	2 mo	32%
Resik 13 [39]	Cuba	4 mo	63%
Intramuscular administration of 2 doses			

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%

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

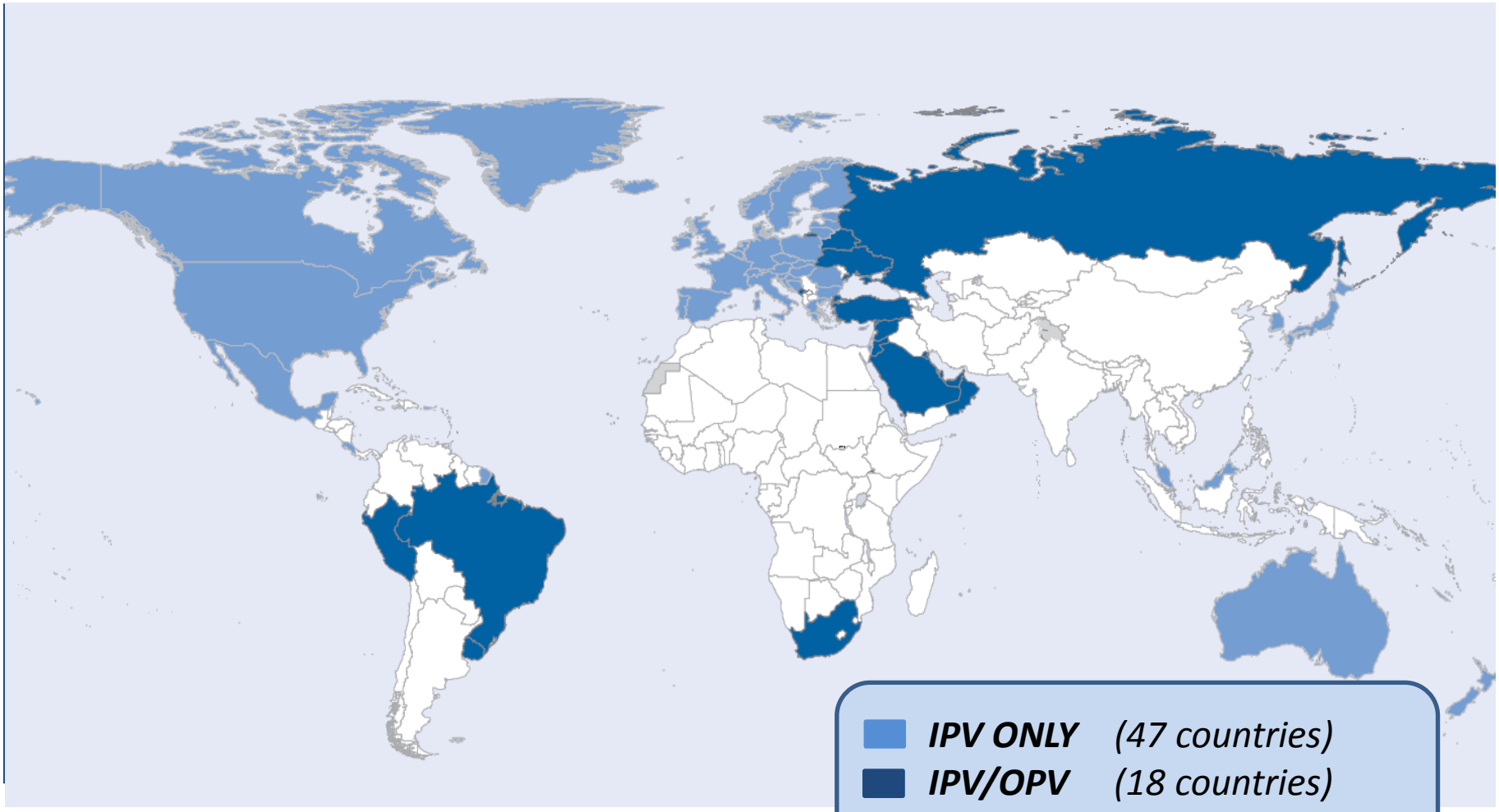
** for current OPV-only countries; the WG is not recommending to change existing schedules*

Issues surrounding immunization policy changes

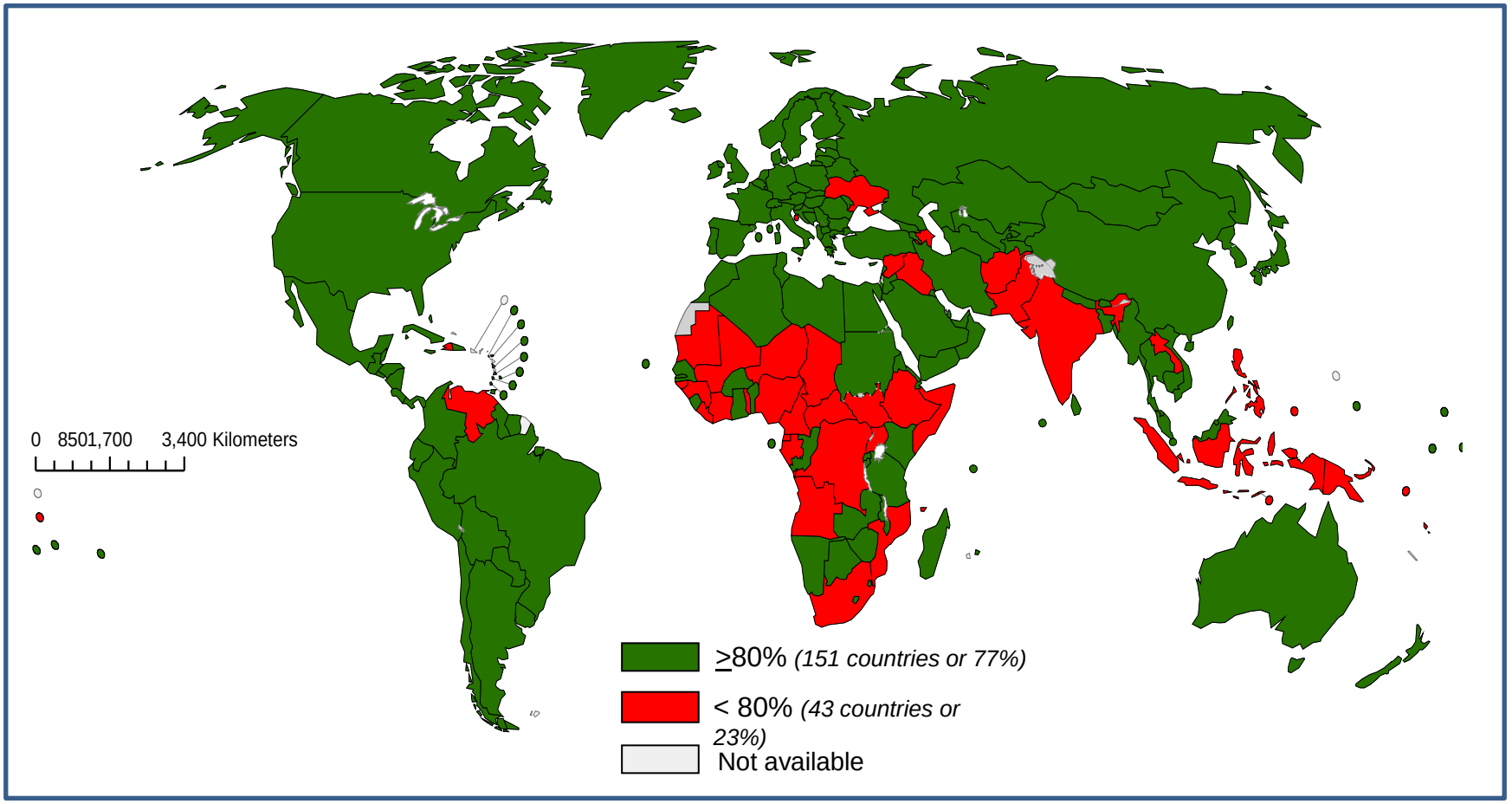
Prerequisites for OPV2 cessation:

- 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 type2
- 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



Issue: DTP3 coverage ≤80%, 2009-11

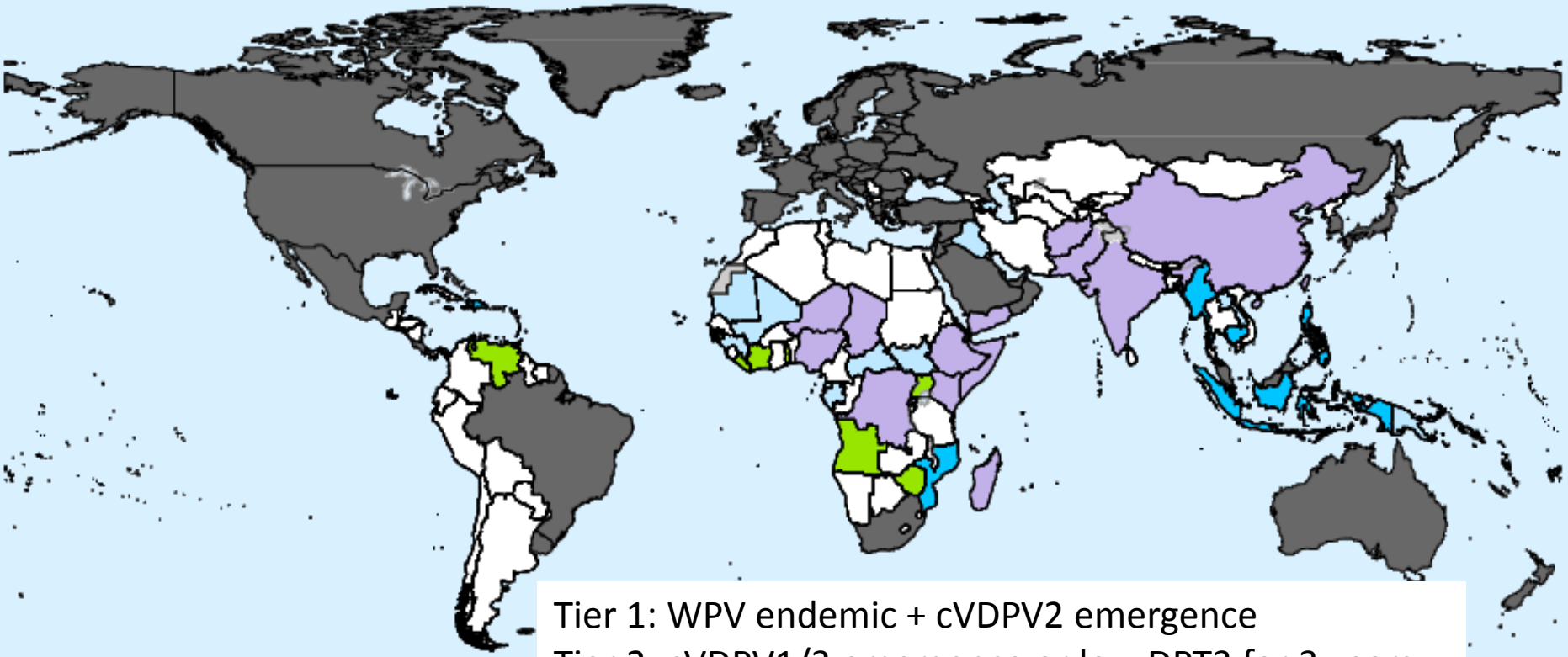


SAGE Working Group: Countries could be prioritized (tiered) for IPV introduction based on cVDPV risk

IPV INTRODUCTION TIERING

Possible country tier for IPV introduction based on endemic status, history of cVDPV emergence, recent DTP3 coverage, and PV importation risk

MAP DATE: 04 July 2013, Version 1.0



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

Map Scale (A3): 1:100,000,000

1 cm = 1,000 km

Coordinate System: GCS WGS 1984
Datum: WGS 1984
Units: Degree

Data Source:
Admin. Boundaries: World Health Organization
Base Map:ESRI
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization
Data as on

Legend:
- *IPV or Sequential routine immunization schedule*
- *Tier 1 Countries (Endemic countries or countries with cVDPV2 emergence)*
- *Tier 2 Countries (Large/medium size countries with history of cVDPV1 and 3)*
- *Tier 2 Countries (DTP3 < 80% In 2009, 2010, and 2011)*
- *Tier 3 Countries (countries with DTP < 80% at least one year 2009-2011)*
- *Other OPV 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

	tOPV	bOPV
GSK, Belgium	29 March 2004	29 October 2009
Sanofi Pasteur, France	16 June 2002	2 August 2011
Bio Farma, Indonesia	9 April 1997	26 May 2010
Novartis, Italy	2 January 1987	10 November 2011
Haffkine, India SIIL, India	2 February 2006 2 April 2013	19 March 2010 4 January 2013

Status of prequalified IPV

Bilthoven Biologicals (NVI), Netherlands	6 December 2010
GSK, Belgium	5 August 2010
Sanofi Pasteur, France	9 December 2005
Statens Serum Institut, Denmark	23 December 2010
Fillers of inactivated trivalent bulks	In the pipeline

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 2: bOPV Primary Series + IPV

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)

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 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 GSK tOPV 6, 10, 14 wks (n=200)

Bangladesh fIPV: Comparison of Fractional, IPV Full, and/or bOPV at 6, 10, and 14 wks
- 3 Sanofi tOPV (6, 10, 14 wks) n=259
- 3 Sanofi bOPV (6, 10, 14 wks) n=259
- 2 BB/SII IPV Full dose IM (6, 14 wks)
- 2 BB/SII IPV Fractional dose ID by nano-pass (6, 14wks) n=194
- 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.

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 bOPV (0, 6, 10, 14 wks) n=180
- 4 Panacea bOPV (0, 6, 10, 14 wks) + 1 Panacea IPV full dose (14 wks) n=180
- 4 Panacea bOPV (0, 6, 10, 14 wks) + 2 Panacea IPV full dose (14 wks and 18 wks) n=180

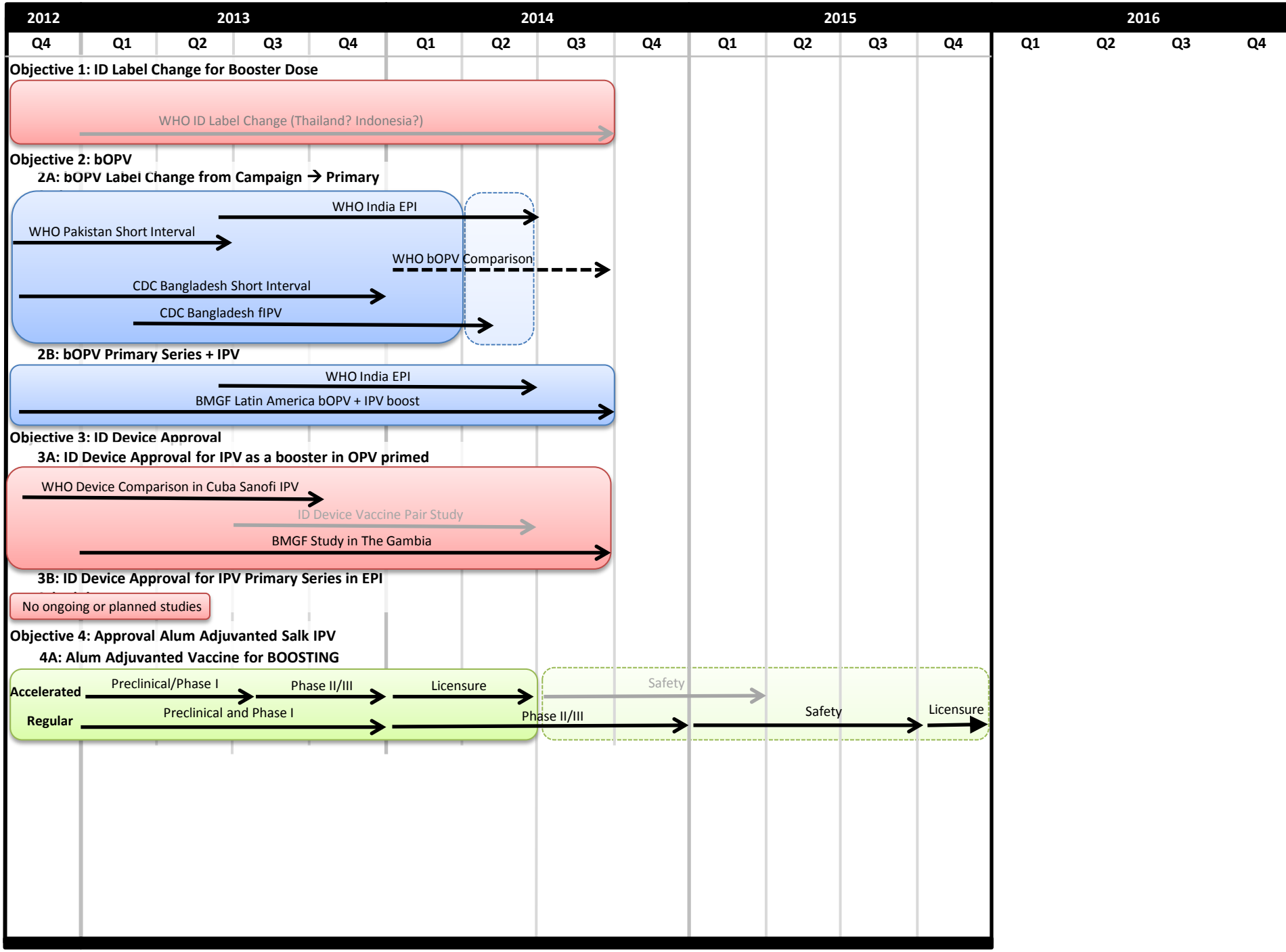
Latin America Full Dose IPV IM boosters in bOPV primed Infants
- 3 Sanofi bOPV (6, 10, 14 wks) n=210
- 3 Sanofi tOPV (6, 10, 14 wks) n=100
- 3 Sanofi bOPV (6, 10, 14 wks) + 1 Sanofi IPV Full Dose IM (14wks) n=210 *+ 1 Sanofi IPV Full Dose IM (9m) n=210*
- 3 Sanofi bOPV (6, 10, 14 wks) + 1 BB/SII IPV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

Bulk	GSK	Sanofi		Bio Farma					Novartis
Filler	GSK	Sanofi	Panacea	Bio Farma	Panacea	Haffkine	Bharat	SII	Novartis
tOPV EPI	Bangla. Short Interval n=200	Latin America n=100 Bangla. fIPV n=259	India bOPV Com		**India EPI n=180**				
bOPV EPI	Bangla. Short Interval n=200 India bOPV Com	Latin America n=210 Bangla. fIPV n=259 India bOPV Com	**India EPI n=180** India bOPV Com	India bOPV Com		India bOPV Com	India bOPV Com	India bOPV Com	India bOPV Com

WHO

	GSK IPV	Sanofi IPV	BB/SII IPV	Panacea (Sanofi)
bOPV Primary Series + IPV IM Full dose (14wks)	Latin America n=50	Latin America n=210	Latin America n=50	**India EPI n=180**
bOPV Primary Series + IPV ID fractional Dose by Needle & Syringe (14wks)				
Other bOPV + IPV Schedules	Latin America n=210	Bangla. fIPV n=259 Latin America n=210	Latin America n=210	

WHO Panning **BMGF**


2012
2013
2014
2015
2016
Q4
Q1
Q2
Q3
Q4
Q1
Q2
Q3
Q4
Q1
Q2
Q3
Q4
Q1
Q2
Q3
Q4
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 India EPI
WHO Pakistan Short Interval
WHO bOPV Comparison
CDC Bangladesh Short Interval
CDC Bangladesh fIPV
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
Safety
Regular
Preclinical and Phase I
Phase II/III
Safety
Licensure

Next steps

SAGE WG: timeframe towards OPV2 withdrawal

11/2013: SAGE recommendations on IPV schedules, draft response protocol, draft IPV supply and financing strategy

5/2014: WHA information paper and possible technical briefing on OPV2 withdrawal

11/2014: SAGE recommendation on final response protocol and potential target date for last OPV2 use

5/2015: WHA resolution on key OPV2 withdrawal issues

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