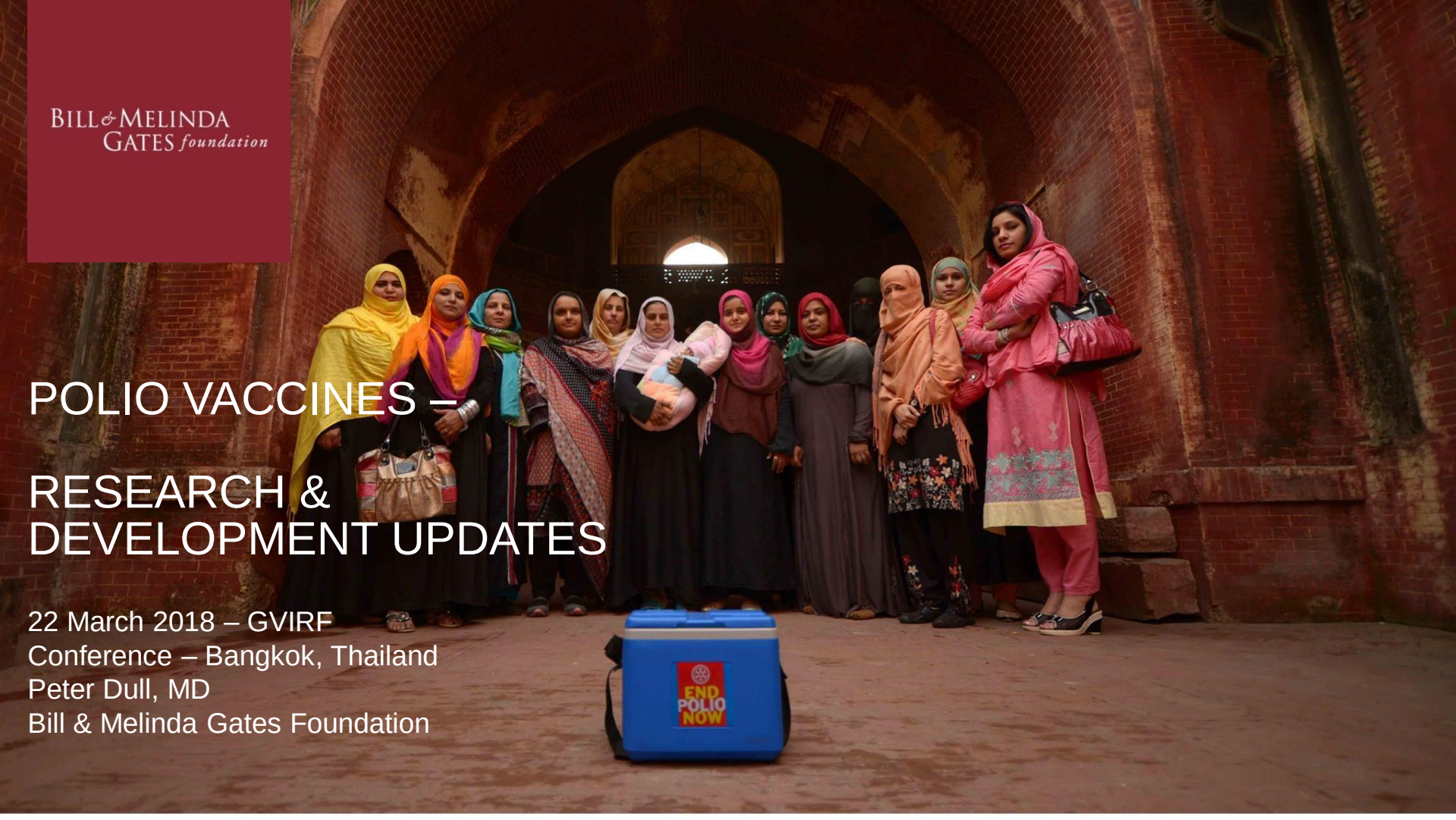


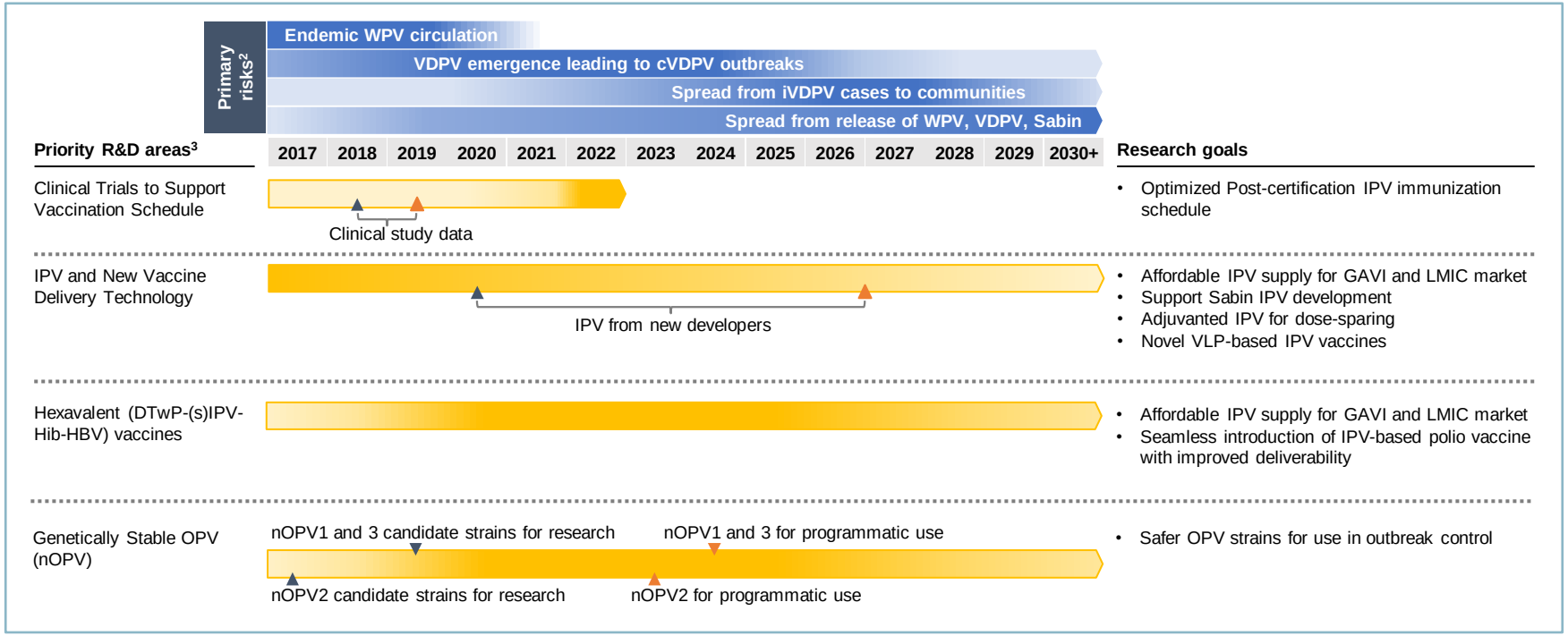
POLIO VACCINES –

RESEARCH & DEVELOPMENT UPDATES

22 March 2018 – GVIRF Conference – Bangkok, Thailand

Peter Dull, MD
Bill & Melinda Gates Foundation

POLIO VACCINE RESEARCH & DEVELOPMENT OVERVIEW



1 R&D to introduce new products may not always be complete before implementation need begins; 2 Timeline of risks assumes current certification timeline – research will continue regardless of certification timeline changes; 3 Specific research projects that are listed are examples, not an exhaustive list; 4 Earliest availability is for compassionate use

ENDGAME POLIO VACCINE CHOICES: KEY R&D ISSUES

1. **Immunogenicity of IPV – bOPV mixed / sequential schedules**
2. **Cost** and **supply** constraints of **IPV**: quest for dose/antigen sparing & improved yield
3. Mitigate all **risks** of **vaccine-related** poliovirus disease/transmission
4. Optimal **IPV schedules and formulations** for **post-OPV cessation** era

Thanks to Ananda Bandyopadhyay (BMGF) for slide support

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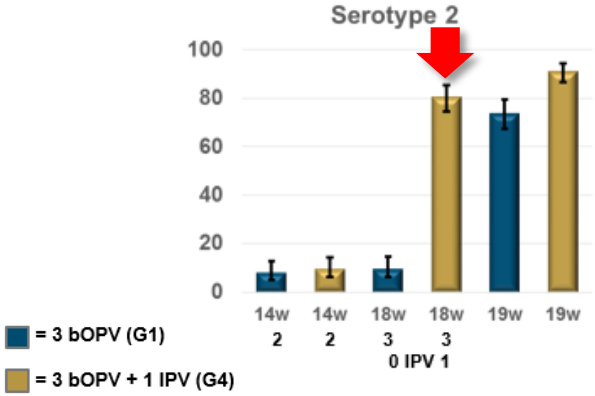
SEROCONVERSION WITH **bOPV** FOLLOWED BY **IPV: LATAM**

Humoral and intestinal immunity induced by new schedules of bivalent oral poliovirus vaccine and one or two doses of inactivated poliovirus vaccine in Latin American infants: an open-label randomised controlled trial

*Edwin J Asturias, Ananda S Bandyopadhyay, Steve Self, Luis Rivera, Xavier Saez-Llorens, Eduardo Lopez, Mario Melgar, James T Gaensbauer, William C Weldon, M Steven Oberste, Bhavesh R Borate, Chris Gast, Ralf Clemens, Walter Orenstein, Miguel O'Ryan G, José Jimeno, Sue Ann Costa Clemens, Joel Ward, Ricardo Rüttimann, and the Latin American IPV001BMG Study Group**

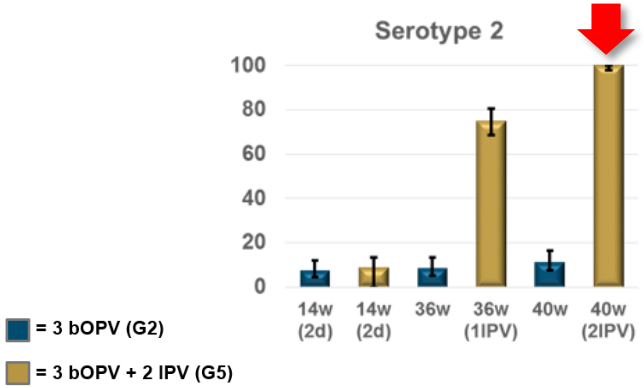
Seroconversion after ≥3 doses of bOPV followed by **1 IPV** dose at 14 weeks(1)



Seroconversion with one dose IPV at 14 weeks: 80%

IPV **administered** at week **14** weeks, and responses measured at 18 weeks

Seroconversion after ≥3 doses of bOPV followed by **2 IPV** doses (2)



Seroconversion with two doses of IPV: 100%

IPV **administered** at week **14 and 36** weeks, and responses measured at 18 and 40 weeks respectively

Asturias, Edwin et al. The Lancet. 2016

HIGH DOSE MONOVALENT TYPE 2 IPV TRIAL: **PANAMA**

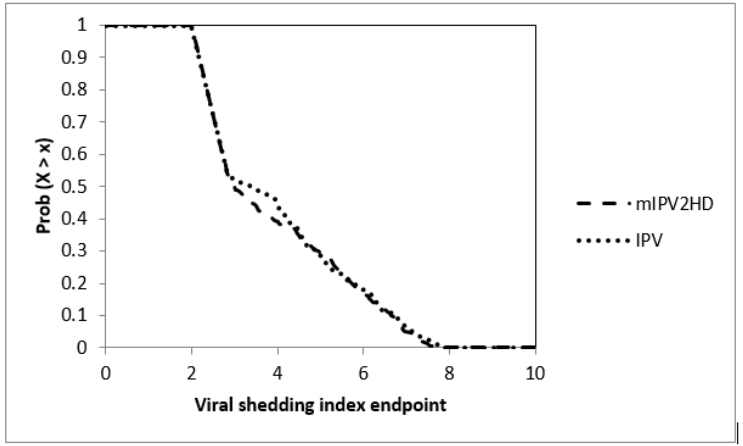
Immunogenicity and safety of a novel monovalent high-dose inactivated poliovirus type 2 vaccine in infants: a comparative, observer-blind, randomised, controlled trial

Xavier Sáez-Llorens, Ralf Clemens, Geert Leroux-Roels, José Jimeno, Sue Ann Costa Clemens, William C Weldon, M Steven Oberste, Natanael Molina, Ananda S Bandyopadhyay

Figure 1: Type-2 Seroconversion 4 weeks following IPV dose

m-IPV2 HD (N=115)		t-IPV (N=115)		Difference	
n/N	% [95% CI]	n/N	% [95% CI]	Value [95% CI]	P-value
107/115	93.0 [86.8-96.9]	86/115	74.8 [65.8-82.4]	18.3 [5.0- 31.1]	< 0.001

Figure 2: Reverse cumulative distribution of type 2 poliovirus shedding index after mOPV2 challenge



Sáez-Llorens, Xavier, et al. The Lancet ID. 2016

IMMUNOGENICITY OF IPV – bOPV SCHEDULES: KEY TAKEAWAYS FROM *RECENT* TRIALS

- **WHO recommended policy of bOPV + ≥ 1 IPV dose for routine immunization will provide**
  - > 90% protection to types **1** and **3**
  - ~80% type-**2** protection after **1** dose of **IPV** at 14 weeks

- **Up to 100% type-2 protection when second IPV dose is given at 9 months of age.**

- **Limited impact of one or two doses of IPV on primary intestinal immunogenicity for type-2 compared to impact of OPVs, irrespective of the primary schedule.**

- **Increasing type-2 D- Ag content of IPV substantially improves seroconversion rates but has limited/no impact on viral shedding.**

Asturias, Edwin et al. The Lancet. (2016); **O'Ryan, Miguel**, et al. The Lancet ID 15.11 (2015): 1273-1282; **Sáez-Llorens, Xavier**, et al. The Lancet ID. (2016): 321-330. **Anand, Abhijeet**, et al. *Vaccine* (2015); **Sutter, Roland W**., et al. *The Lancet* (2015).

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POLIO VACCINE RESEARCH – FUTURE TOOLS

OVERVIEW OF PRODUCTS UNDER DEVELOPMENT

Research question/tool	Importance	Status
IPV **adjuvants**	Reduced cost Increased supply Potential for enhanced mucosal immunity	Clinical studies being implemented to evaluate aluminum salts/other adjuvants for IPV
Novel routes of IPV administration	Operational advantages Potential dose-sparing Use in SIAs; Concomitant use with other vaccines	Studies being planned/implemented with disposable jet injectors, micro needle patch. Technical and cost barriers remain for novel delivery approaches
Genetically stable OPV (nOPV)	Outbreak control (reduced risk of VDPVs and VAPP) or in routine immunization	Human clinical trials began in 2017: results expected in first half of 2018

Bandyopadhyay, Ananda S., et al. "Polio vaccination: past, present and future." Future microbiology 10.5 (2015): 791-808.

ALUM-ADJUVANTED IPV – DOSE-SPARING

STUDY FROM DOMINICAN REPUBLIC AFTER 6.10.14W INFANT SERIES

Immunogenicity results for poliovirus type 1

	1/3 IPV-Al (n=205)	1/5 IPV-Al (n=205)	1/10 IPV-Al (n=204)	IPV (n=206)	Total (n=820)
Prevaccination visit 1					
Mean (GMT)	13·0 (10·2–16·4)	10·4 (8·5–12·9)	12·7 (10·1–15·8)	14·4 (11·5–18·1)	12·5 (11·2–14·0)
Median	11·3	11·3	11·3	16·0	11·3
Seroprotection*	125 (61·0%)	120 (58·5%)	125 (61·3%)	128 (62·1%)	498 (60·7%)
Post-second vaccination visit 3 (exploratory)					
Mean (GMT)	1030·9 (778·7–1364·9)	637·8 (476·0–854·7)	432·0 (330·9–564·0)	2557·3 (2091·0–3127·5)	NA
Median	1448·2	724·1	512·0	2896·3	NA
Seroprotection*	200 (97·6%)	196 (95·6%)	195 (95·6%)	206 (100·0%)	NA
Seroconversion (primary outcome)†	187 (91·2%)	188 (91·7%)	182 (89·2%)	197 (95·6%)	NA
Seroconversion‡	190 (92·7%)	197 (96·1%)	191 (93·6%)	197 (95·6%)	NA
Post-third vaccination visit 4					
Mean (GMT)	3310·2 (2738·2–4001·5)	2221·1 (1808·9–2727·3)	1584·6 (1277·8–1965·1)	3727·7 (3211·1–4327·4)	NA
Median	4096·0	2896·3	1448·2	4096·0	NA
Seroprotection*	204 (99·5%)	204 (99·5%)	204 (100%)	206 (100%)	NA
Seroconversion (primary outcome)†	202 (98·5%)	204 (99·5%)	201 (98·5%)	206 (100%)	NA
Seroconversion‡	203 (99·0%)	204 (99·5%)	201 (98·5%)	206 (100%)	NA

Data are for per-protocol population. IPV=inactivated polio vaccine. IPV-Al= IPV adsorbed to aluminium hydroxide. GMT=geometric mean concentration

Rivera et al. Lancet ID. April 2017.

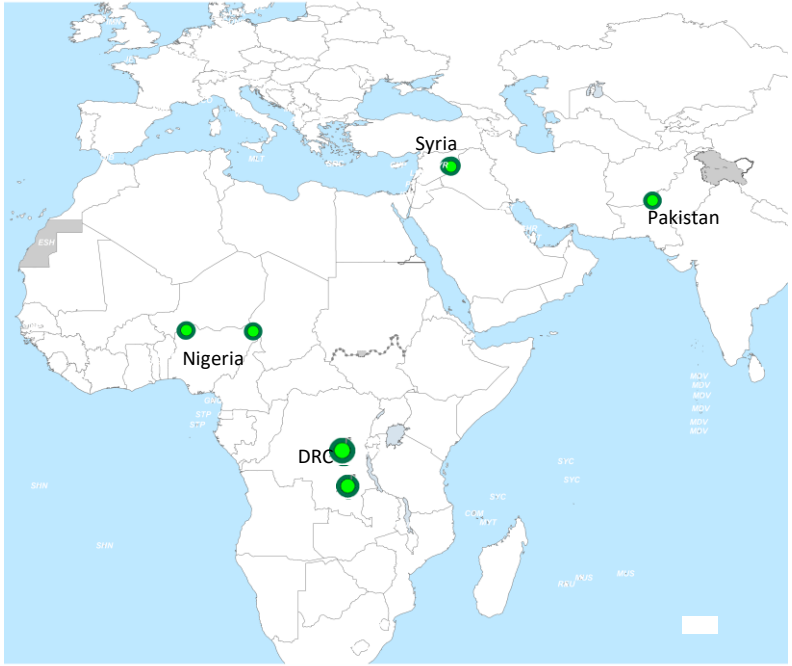
FRACTIONAL DOSE IPV – 2-DOSE IMMUNOGENICITY

OVERVIEW OF AVAILABLE CLINICAL DATA

Country, Field-work	IPV type & schedule	Type 2 seroconversion (SC), (95%CI)	Type 2 SC (fIPV- IPV)	P-value	Seroconversion & priming*
Cuba, 2006-07	IPV (6 weeks)	36 (29-43)	19	<0.001	-
	fIPV (6, 10 weeks)	55 (48-62)			-
Oman, 2007	IPV (2 months)	32 (25-39)	40	<0.001	-
	fIPV (2, 4 months)	72 (66-78)			-
Cuba, 2009-10	IPV (4 months)	63 (55-70)	35	<0.001	99
	fIPV (4, 8 months)	98 (94-99)			97
Bangladesh, 2012-13	IPV (6 weeks)	38 (31-46)	43	<0.001	90
	fIPV (6, 14 weeks)	81 (74-86)			78
Bangladesh, 2014-15	IPV (14 weeks)	74 (68-78)	NA	-	-

Anand, Abhijeet, et al. "Immunogenicity to poliovirus type 2 following two doses of fractional intradermal inactivated poliovirus vaccine: A novel dose sparing immunization schedule." *Vaccine* (2017).

Post switch cVDPV2 outbreaks
(1 May 2016 – 31 December 2017 [20 months])



6 cVDPV2 outbreaks reported after the switch, from 4 countries:
[case=paralytic manifestation]

1. **Pakistan** (1 case, Quetta)
2. **Nigeria Borno** (1 case)
3. **Nigeria Sokoto** (1 case)
4. **DRC Maniema** (2 cases)
5. **DRC Haut Lomami and Tanganyika** (15 cases)
6. **Syria** (74 cases, mostly Deir ez-Zor)

Using assumption of 1%nt change/year at a uniform rate, all VDPV2 except DRC, Maniema seeded before the switch.

NOVEL OPV2 DEVELOPMENT

Objective: To reduce the risk of vaccine associated paralytic poliomyelitis (**VAPP**) and circulating vaccine derived polioviruses (**cVDPV**) when deployed in response to a type 2 cVDPV outbreak occurring after global discontinuation of OPV2.

Status:

- Two nOPV2 candidates designed to improve **genetic stability** and decrease the risk of loss of attenuation relative to the parental Sabin 2 strain
- After passage under conditions which promote loss of attenuating mutations, both candidates appear **less prone to reversion to neurovirulence** according to:
  - Deep sequencing
  - Transgenic mouse neurovirulence assay
- **First-in-human** clinical trial under **contained** conditions **completed** in Antwerp, Belgium in **2017**.

NOVEL OPV2 DEVELOPMENT - BIOCONTAINMENT

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POST-OPV ERA: **SAGE** RECOMMENDATIONS: **APRIL 2017**

- Countries should include at least **two doses of IPV** in their routine immunization schedule, the first at or after 14 weeks (e.g. with the 2nd or 3rd dose of DTP-containing vaccine) and the second dose ≥4 months after the first dose, administered either as full or fractional doses;
- Countries without Poliovirus Essential Facilities (PEFs) should maintain IPV in their routine immunization schedule for **at least 10 years after global OPV withdrawal**, to address: immediate (VDPVs), intermediate (iVDPV) and longer-term (e.g. containment failure) risks;
- Countries with PEFs should continue to use IPV as long as mandated by the Global Action Plan to minimize poliovirus facility-associated risk (GAP III).

EVALUATION OF OPTIMAL DOSING REGIMEN FOR STAND-ALONE IPV-ONLY INFANT VACCINATION

INITIATED ENROLLMENT OCTOBER 2017 IN PANAMA AND DOM REPUBLIC

Vaccine Route	Arm	Vaccination (weeks)	Serology (weeks)
Intramuscular IPV	A	10-14-36	10-14-18-40
	B	14-36	14-18-36-40
Intradermal f-IPV	C	10-14-36	10-14-18-40
	D	14-36	14-18-36-40

Clinicaltrials.gov: NCT03239496 **Results:** Q1 2019

WCP-BASED IPV-HEXA VACCINES ARE COMING

Criteria	Penta + IPV	Hexavalent
Immunogenicity	▪ Seroconversion after 2 doses at 14 weeks + 9 months (SAGE) recommended and currently under study (f-IPV and full-dose IPV)	▪ Seroconversion after 3 doses at 6, 10, 14 weeks tbd. ▪ Further IPV dose-sparing possible ▪ No fx dose IPV option

Coverage	▪ Global MV1 coverage = 85%*
	  ▪ AFRO 73%
	  ▪ EMRO 77%
		▪ Global DTP3 coverage = 86%*
		  ▪ AFRO 77%
		  ▪ EMRO 82%

Premature IPV cessation in countries without polio essential facilities	▪ Higher risk	▪ Lower risk
Flexibility to drop IPV from vaccination after 10 years	▪ Highly flexible option	▪ Product locked in ▪ Ongoing opportunity costs
Flexibility for campaign use	▪ Highly flexible option	▪ Cannot use IPV for campaigns
Number of injections	▪ 5 in 4 visits	▪ 3 in 3 visits
Supply considerations:	▪ Hexa and stand-alone IPV doses pull from same sources	

* WHO/UNICEF coverage estimates 2014 revision. July 2015 Immunization Vaccines and Biologicals, (IVB), World Health Organization

CONCLUSIONS

- Polio vaccine development remains very active and complex with many uncertainties
- “Old vaccines” with many new and unanswered questions during a unique peri- and post-eradication period
- Critical period for polio type 2 immunogenicity with withdrawal of OPV2 from routine use
- New innovations required to address challenges
  - Optimal schedules with existing mix of vaccines and routes of administration
  - New IPVs due to supply and cost constraints
  - Combination products to address delivery complexities
  - Readiness for outbreak response post-OPV discontinuation


THANK YOU

BACK-UP

GENERATION OF A VIRUS-FREE POLIO VACCINE

Rationale: To produce polio vaccines equivalent to current IPV in performance without the need to grow the virus.

Need: To reduce risk of release of replication competent virus in the post-eradication era.

Approach: To produce poliovirus empty particles (VLPs) by recombinant expression in yeast, mammalian, insect, plant or prokaryotic systems.

Problem: Empty particles are less antigenically stable than virus and readily convert from the desired N (or D) form to the inappropriate H (or C) form unless kept cold or in the presence of stabilising 'pocket' binding drugs.

Solution: Introduce stabilising mutations into the capsid protein

Consortium includes: University of Leeds, University of Oxford, University of Reading, National Institute for Biological Standards and Control, John Innes Centre

Poliovirus VLP vaccines: progress and problems

Achievements:

- Thermostable and D reactive empty capsids (VLPs) of each poliovirus serotype have been developed.
- Long term stability at 37^0 superior to IPV.
- Thermostable VLPs have equivalent/greater immunogenicity cf. IPVs.
- Thermostable VLPs can be produced by recombinant expression.

Technical challenges:

- Understand and control particle assembly in different expression systems.
- Optimise VLP extraction procedures.
- Refine and simplify purification methods.

Development Challenge:

- Timing of availability relative to other vaccine ‘solutions’ and business model for development requires further evaluation