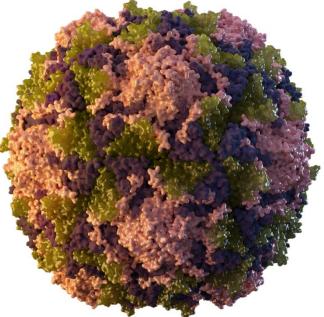
Centers for Disease Control and Prevention National Center for Immunization and Respiratory Diseases



Clinical Considerations for Children who Received Fractional Dose Inactivated Polio Vaccine (fIPV) in Other Countries

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Background

Wild poliovirus type 2 eradicated in 2015

- Global switch and withdrawal of Sabin type 2 virus from OPV in April 2016:
 - Replaced all trivalent OPV (tOPV; types 1, 2, and 3) with bivalent OPV (bOPV; types 1 and 3)
 - − ≥1 dose IPV recommended as part of routine immunization in all countries using bOPV
- Based on clinical trial data and limited IPV availability, WHO supports use of 2 fractional doses of IPV (1/5 full dose IPV) given intradermally in place of single full IPV dose (intramuscular)

WHO. World Epidemiological Record 2016;91:561-82.

WHO. World Epidemiological Record 2021;96:613–32.

https://www.who.int/teams/immunization-vaccines-and-biologicals/diseases/poliomyelitis-(polio)

ONE fractional IPV (fIPV) dose is LESS immunogenic than one full IPV dose

Meta-analysis of percent that seroconverted for poliovirus type 2 (Mashunye 2021)

	One dose of fIPV (n/N)	One dose of full-dose IPV (n/N)	Weight (%)		Risk ratio (95% CI)
Study or subgroup					
Anand et al ³³	30/164	62/162	10.2	_	0.48 (0.33-0.70)
Clarke et al ³⁶	177/368	299/365	17.6	-=-	0.77 (0.67-0.88)
Estivariz et al ³¹	21/49	35/50	10.4	_	0.61 (0.42-0.89)
Mohammed et al ²⁹	31/200	57/200	9.9	e	0.54 (0.37-0.80)
Resik et al ²⁸	35/235	63/236	10.4	_	0.56 (0.38-0.81)
Resik et al ³²	74/160	96/160	15.3		0.77 (0.63-0.95)
Resik et al ³⁴	164/375	80/91	17.4		0.50 (0.43-0.57)
Resik et al ³⁹	14/30	20/26	8.8		0.61 (0.39–0.94)
Total (95% CI)	1581	1290	100-0	\diamond	0.61 (0.51–0.72)
Total events	546	642		× I	
Heterogeneity: τ²=0·0	4, χ²=26·27, df=7 ((p=0·0004); ₽°=74%	6		
Test for overall effect:	Z=5·59 (p<0·000	01)			
				0.1 0.2 0.5 1 2	5 10
				Favours full dose Favours fractional dos	e

Mashunye et al. Lancet Infect Dis 2021;21:1161–74.

TWO fractional IPV (fIPV) doses are MORE immunogenic than one full IPV dose

90 80 70 * 60 * 50 * * 40 * * 30 20 10 0 Type 1 Type 2 Type 3

Percent with seroconversion at 18 weeks

■ 2 fIPV 6 & 14 wk ■ 1 IPV 6 wk ■ 1 IPV 14 wk

* P< 0.01 versus 2 fIPV doses

Slide adapted from Concepcion Estivariz. Data from Snider et al. Lancet 2019; 393:2624.

Current Use of fIPV in Routine Immunization Globally

- Gountries (~20% of global birth cohort) use 2 fIPV doses + ≥3 bOPV doses in routine childhood immunization schedule
 - Bangladesh, Cuba, Ecuador, India, Nepal, Sri Lanka

Example polio vaccination schedule (India):

	Birth	6 weeks	10 weeks	14 weeks	16–24 months	Total doses
bOPV	Х	Х	Х	Х	Х	5 bOPV
fIPV		Х		Х		2 fIPV

Current US Guidance

- Recommended polio vaccination
 - 4 total IPV doses, administered at 2, 4, 6–18 months, and 4–6 years OR
 - 3 total IPV doses if 3rd dose administered after 4th birthday and ≥6 months after 2nd dose
- For vaccines administered outside of US
 - Only tOPV or IPV doses considered valid for US vaccination schedule

Example polio vaccination schedule (India):

	Birth	6 weeks	10 weeks	14 weeks	16–24 months	Total doses
bOPV	Х	Х	Х	Х	Х	5 bOPV
fIPV		Х		Х		2 fIPV

Current US guidance:

- None of these doses considered valid in US
- Needs 3–4 full IPV doses in US

Question for Work Group:

Should 2 fractional IPV doses administered outside of the United States be counted as either 1 or 2 doses towards the US vaccination schedule?

Methods: Updated Meta-Analysis

- Previous meta-analysis published in 2021 (Mashunye et al)
- Literature review using same search terms; searched Medline, Embase, Cochrane Library, Scopus, and ClinicalTrials.gov
 - Randomized clinical trials
 - Compared 2 fIPV doses to either 1 or 2 IPV doses
 - Published between January 1, 2019 and June 30, 2023

Outcomes

- Seroconversion for poliovirus type 2
 - Change from seronegative (titer <1:8) to seropositive (titer ≥1:8) OR
 - ≥4-fold increase in antibody titer over expected decline in maternal antibodies
- Changes in geometric mean titers

Seroconversion: 2 fIPV Doses vs. 1 IPV Dose

	2 fIP	2 fIPV 1 IPV		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Ahmad 2022 (1)	475	600	132	199	12.1%	1.19 [1.07, 1.33]	
Anand 2015 (2)	123	164	62	162	10.5%	1.96 [1.58, 2.43]	
Aziz 2022 (3)	142	150	129	150	12.4%	1.10 [1.02, 1.19]	-
Mohammed 2010 (4)	134	200	57	200	10.0%	2.35 [1.85, 2.99]	
Resik 2010 (5)	103	235	63	236	9.8%	1.64 [1.27, 2.12]	
Resik 2013 (6)	154	160	96	160	11.8%	1.60 [1.41, 1.83]	-
Resik 2020 (7)	26	30	20	26	9.8%	1.13 [0.87, 1.45]	
Saleem 2021 (8)	88	89	58	81	11.7%	1.38 [1.20, 1.59]	-
Snider 2019 (9)	173	284	249	574	11.8%	1.40 [1.23, 1.60]	-
Total (95% CI)		1912		1788	100.0%	1.47 [1.24, 1.73]	◆
Total events	1418		866				
Heterogeneity: Tau ² = 0.06; Chi ² = 94.08, df = 8 (P < 0.00001); I ² = 91%							
Test for overall effect: Z = 4.56 (P < 0.00001)							0.1 0.2 0.5 1 2 5 10 Favors IPV Favors fIPV

Seroconversion: 2 fIPV Doses vs. 2 IPV Doses

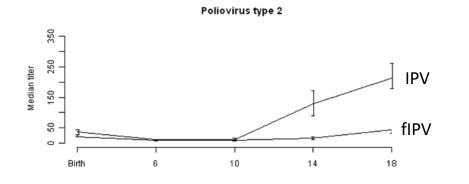
	2 fIP	v	2 IPV		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Resik 2010 (1)	103	235	134	236	7.2%	0.77 [0.64, 0.93]	
Anand 2015 (2)	123	164	142	162	10.8%	0.86 [0.77, 0.95]	
Mohammed 2010 (3)	134	200	163	200	10.2%	0.82 [0.73, 0.92]	
Bandyopadhyay 2021a (4)	135	178	169	200	11.0%	0.90 [0.81, 0.99]	
Resik 2013 (5)	154	160	153	160	13.5%	1.01 [0.96, 1.05]	+
Resik 2020 (6)	26	30	26	26	8.4%	0.87 [0.75, 1.02]	
Bandyopadhyay 2021b (7)	190	217	153	178	12.2%	1.02 [0.94, 1.10]	+
Saleem 2021 (8)	88	89	81	81	13.9%	0.99 [0.96, 1.02]	+
Aziz 2022 (9)	142	150	137	150	12.8%	1.04 [0.97, 1.10]	+
Total (95% CI)		1423		1393	100.0%	0.93 [0.87, 1.00]	•
Total events	1095		1158				
Heterogeneity: Tau ² = 0.01; Chi ² = 63.89, df = 8 (P < 0.00001); I ² = 87%							
Test for overall effect: Z = 2.04 (P = 0.04)							0.2 0.5 1 2 5 Favors 2 IPV Favors 2 fIPV

Seroconversion: 2 fIPV doses are less favorable vs. 2 IPV doses when given at younger age

	2 fIP	V	2 IP	v		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95	% CI Age
Resik 2010 (1)	103	235	134	236	7.2%	0.77 [0.64, 0.93]		6 and 10 weeks
Anand 2015 (2)	123	164	142	162	10.8%	0.86 [0.77, 0.95]		6 and 14 weeks
Mohammed 2010 (3)	134	200	163	200	10.2%	0.82 [0.73, 0.92]		2 and 4 months
Bandyopadhyay 2021a (4)	135	178	169	200	11.0%	0.90 [0.81, 0.99]		10 and 14 weeks
Resik 2013 (5)	154	160	153	160	13.5%	1.01 [0.96, 1.05]	+	4 and 8 months
Resik 2020 (6)	26	30	26	26	8.4%	0.87 [0.75, 1.02]		4 and 8 months
Bandyopadhyay 2021b (7)	190	217	153	178	12.2%	1.02 [0.94, 1.10]	+	14 weeks and 36 week
Saleem 2021 (8)	88	89	81	81	13.9%	0.99 [0.96, 1.02]	+	14 weeks and 9 month
Aziz 2022 (9)	142	150	137	150	12.8%	1.04 [0.97, 1.10]	+	3 and 11–15 months
Total (95% CI)		1423		1393	100.0%	0.93 [0.87, 1.00]	•	
Total events	1095		1158					
Heterogeneity: Tau ² = 0.01; 0	Chi ² = 63.	89, df=	8 (P < 0.	.00001)); I ² = 87%		0.2 0.5 1	<u> </u>
Test for overall effect: Z = 2.04 (P = 0.04)					-			s 2 fIPV

Median Antibody Titers Lower After 2 fIPV vs. 2 IPV Doses

Resik 2010 (3 doses at 6, 10, and 14 weeks)

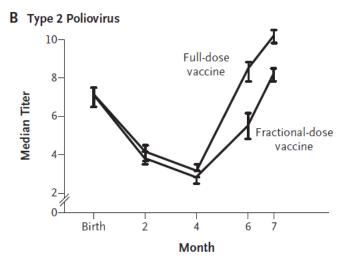


Resik 2020 (2 doses at 4 and 8 months)

Type 2



Mohammed 2010 (3 doses at 2, 4, and 6 months)



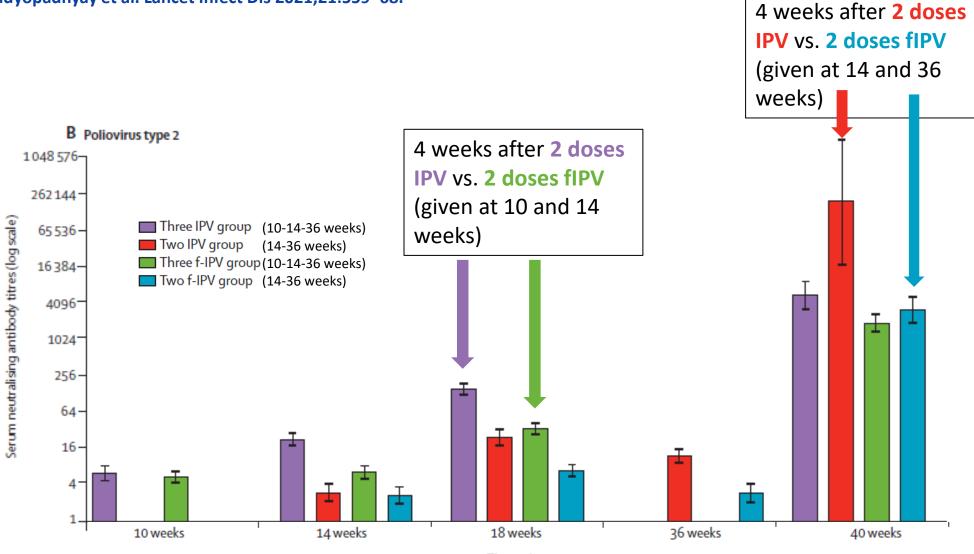
Resik 2013 and Aziz 2022: Median titer (95% CI) after 2 doses

	Age	fIPV	IPV
Resik 2013	4 and 8 months	898 (713-≥1448)	≥1448 (≥1448-≥1448)
Aziz 2022	9-13 and 11-15 months	455 (362-724)	≥1448 (1152-≥1448)

Resik et al, J Infect Dis 2010; Resik et al, J Infect Dis 2020; Mohammed et al, N Engl J Med 2010; Resik et al, N Engl J Med 201; Aziz et al, J Infect Dis 2022.

Geometric Mean Titers: 2 fIPV vs. 2 IPV Doses

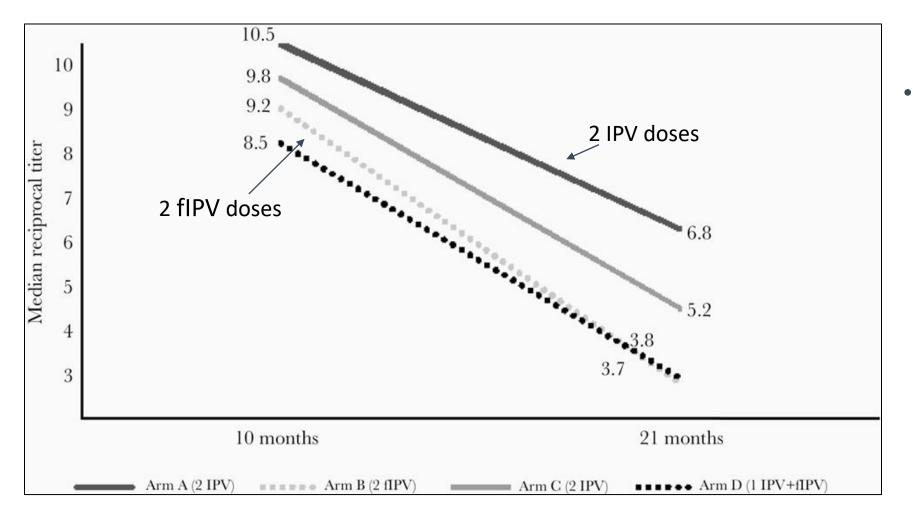
Bandyopadhyay et al. Lancet Infect Dis 2021;21:559-68.





Persistence of Poliovirus Type 2 Antibodies Following 2 fIPV or 2 IPV Doses

Saleem et al. JID 2021; 223(7)1214



As immunization series with fIPV reach lower final titers, seronegativity expected to be reached earlier

Slide adapted from Concepcion Estivariz.



- WHO supports the use of 2 fIPV doses in place of 1 IPV dose as an IPV conservation strategy
- 2 fIPV doses associated with higher rates of seroconversion vs. 1 IPV dose
- 2 fIPV doses associated with slightly lower rates of seroconversion vs. 2 IPV doses
 - Especially when administered at 6 and 14 weeks; rates of seroconversion approach equivalency at older ages of administration
- Peak antibody titers are lower after 2 fIPV doses vs. 2 IPV doses

Proposed CDC Clinical Considerations

- For persons who received fractional (1/5 full dose) IPV administered intradermally outside of the United States, 2 fractional doses of IPV (fIPV) should be considered valid and counted as 1 full intramuscular dose of IPV towards the US vaccination schedule.
- If a person received only 1 dose of fIPV, this dose should not be considered valid or counted towards the US vaccination schedule.

Questions and Discussion

Polio Work Group Members

- ACIP voting members
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 - Lynn Bahta
 - Sybil Cineas

Liaisons

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