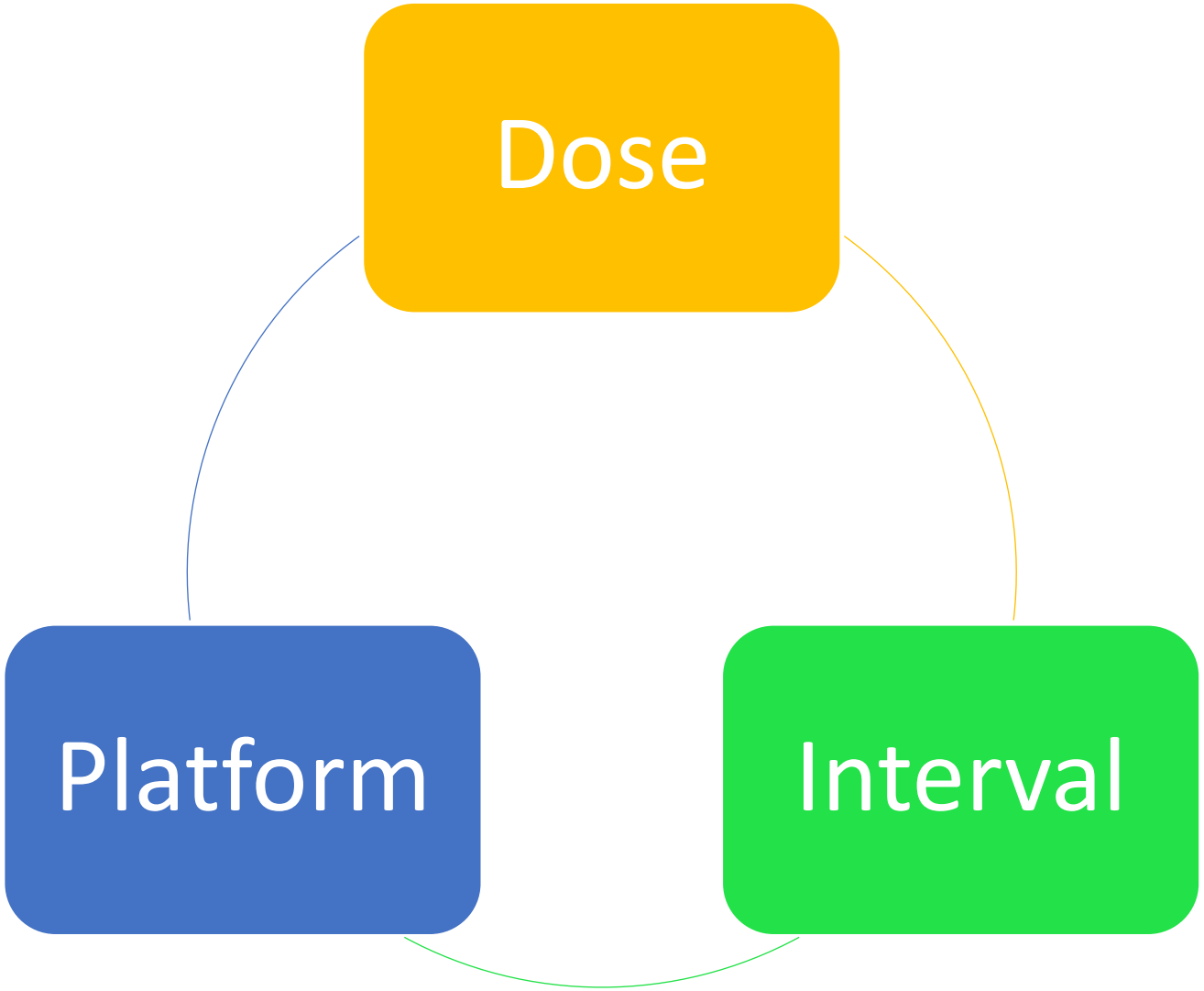
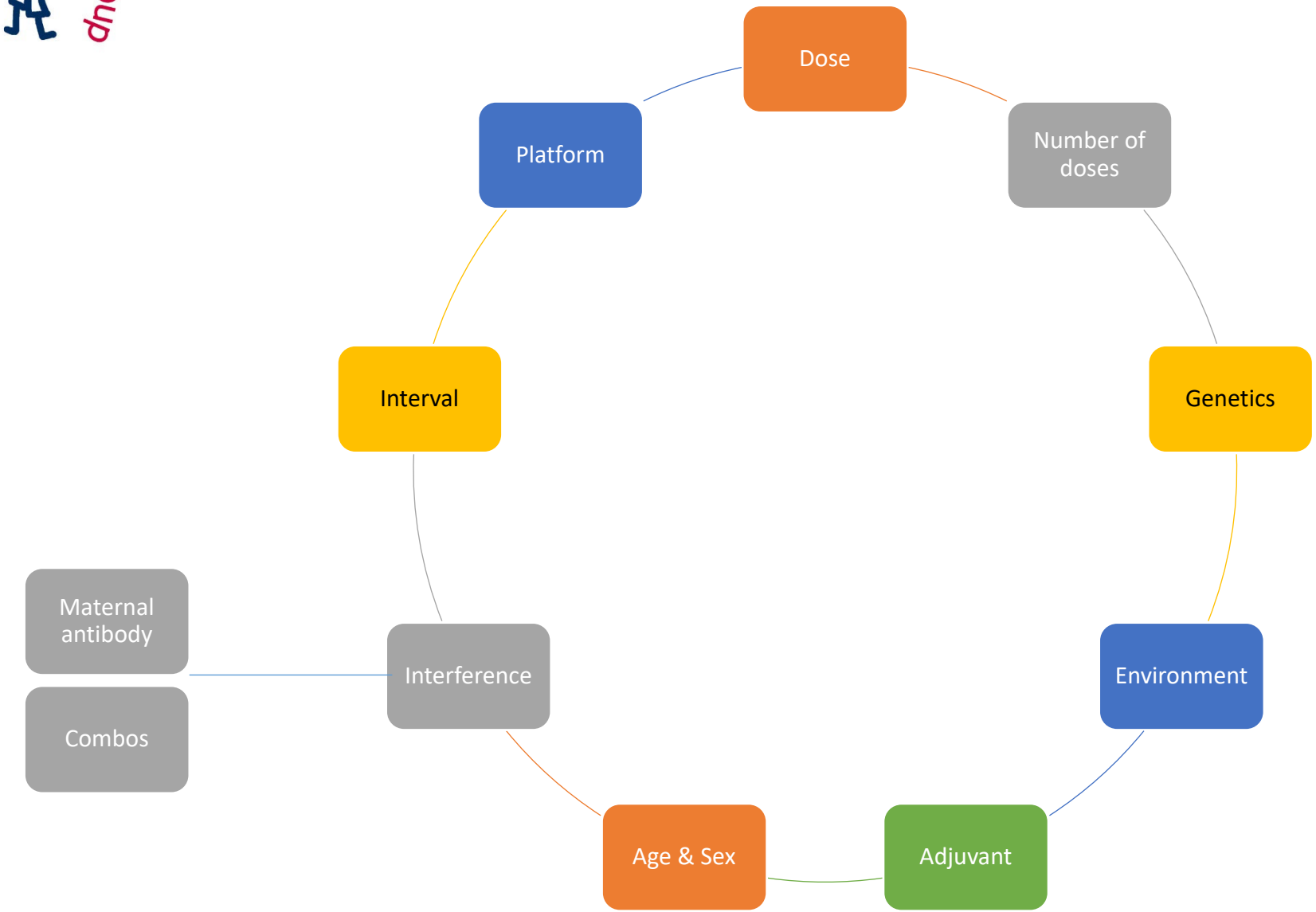
Impact on immunogenicity: dose, dose interval and platform

Andrew J Pollard


Dose
Platform
Interval


Dose
Number of doses
Genetics
Environment
Adjuvant
Age & Sex
Interference
Maternal antibody
Combos
Interval
Platform

Twin studies of genetic contribution to variation in immune response

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Influence of genetic and environmental factors on the immunogenicity of Hib vaccine in Gambian twins

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Environment

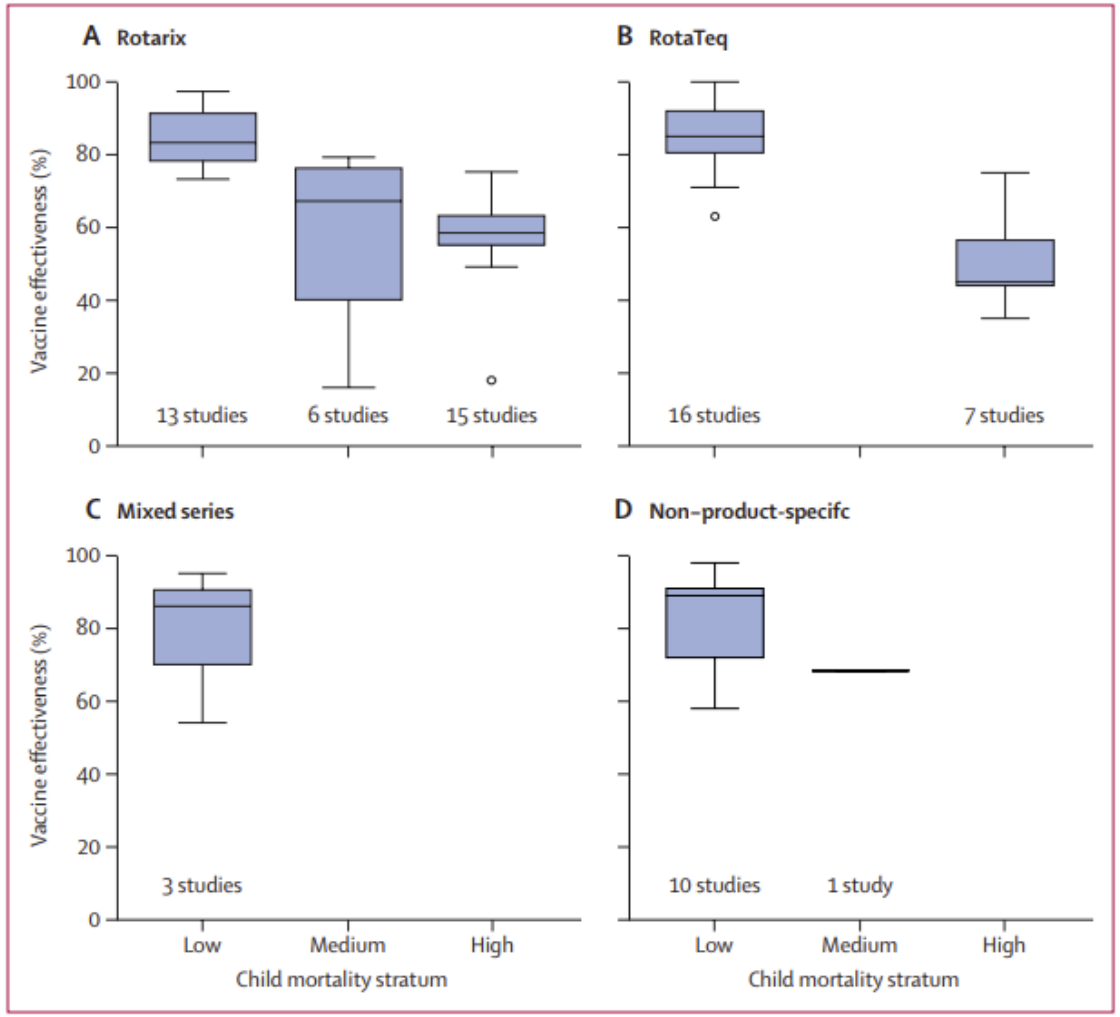
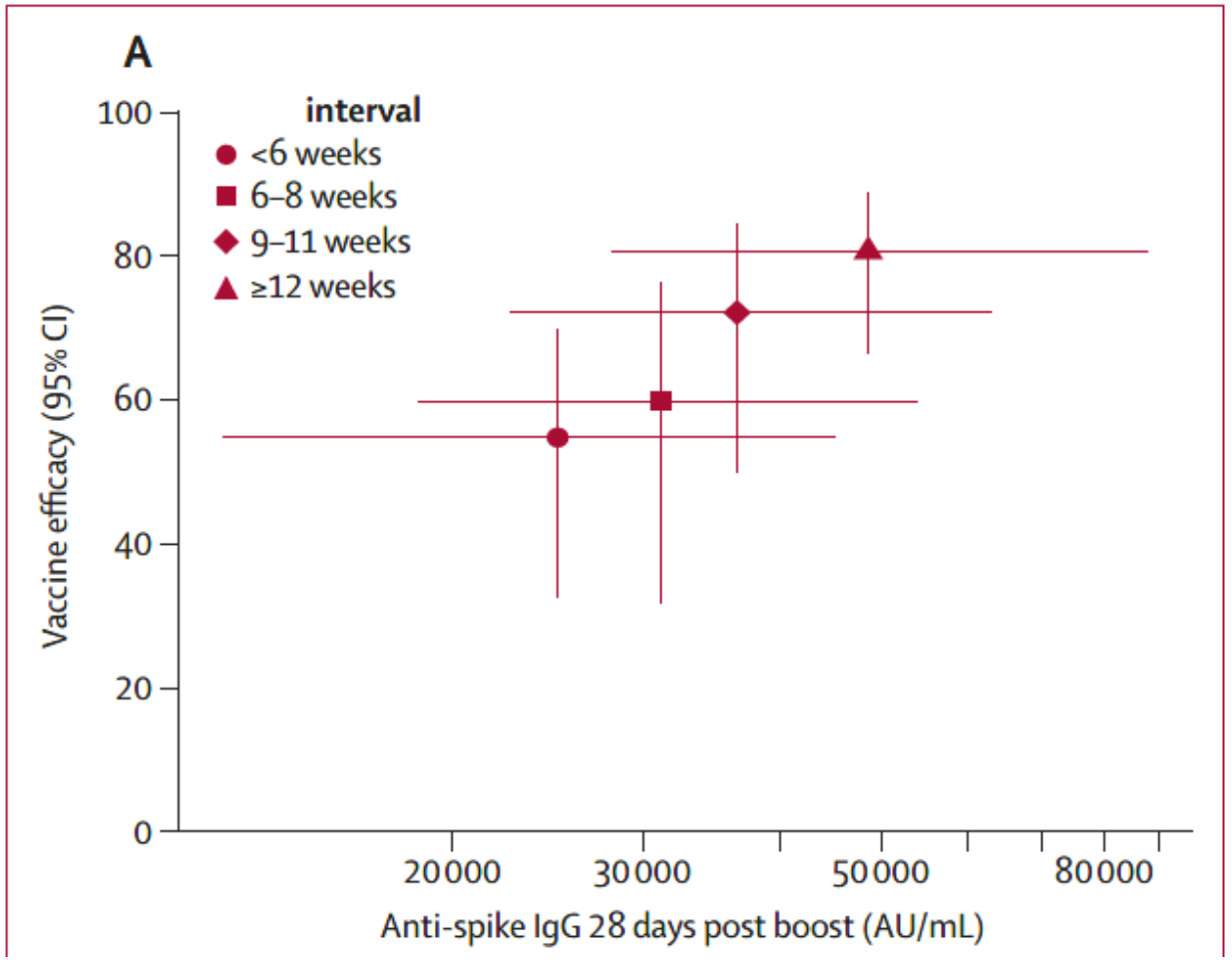


Figure 2: **Rotavirus vaccine effectiveness estimates by vaccine type and child mortality stratum**
Data are presented as medians with IQRs. Circles indicate outliers.

Burnett et al, Lancet GH 2020

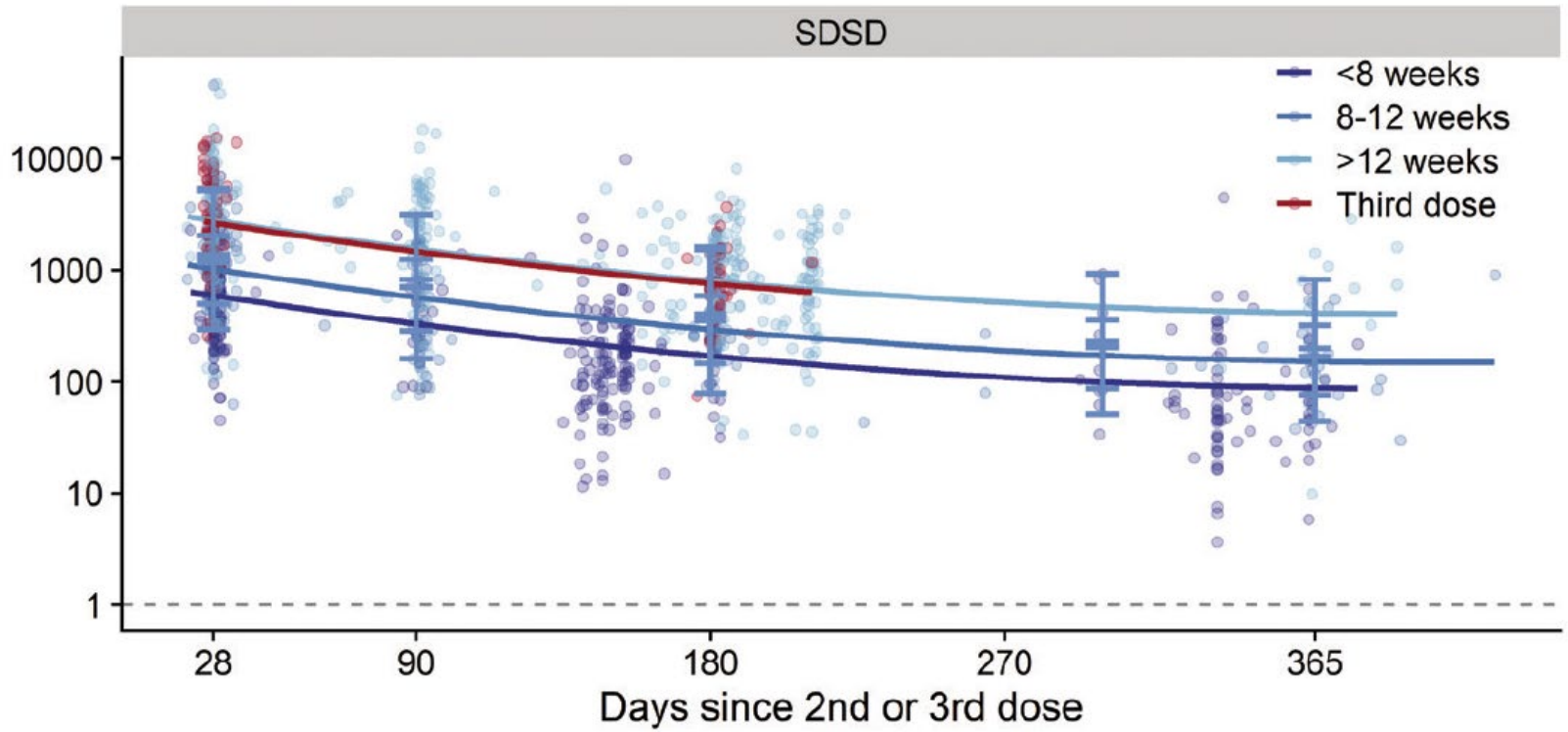
Interval

Interval and COVID19 vaccine efficacy against mild infection



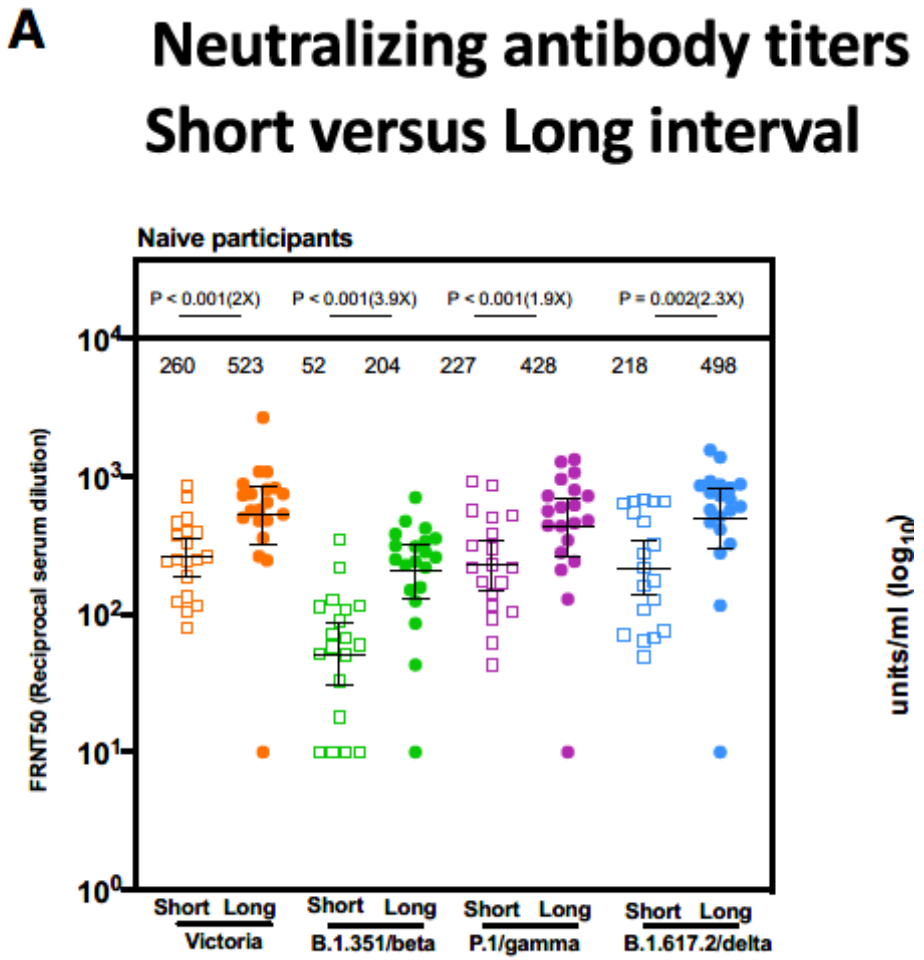
Voysey et al, Lancet 2021

IgG



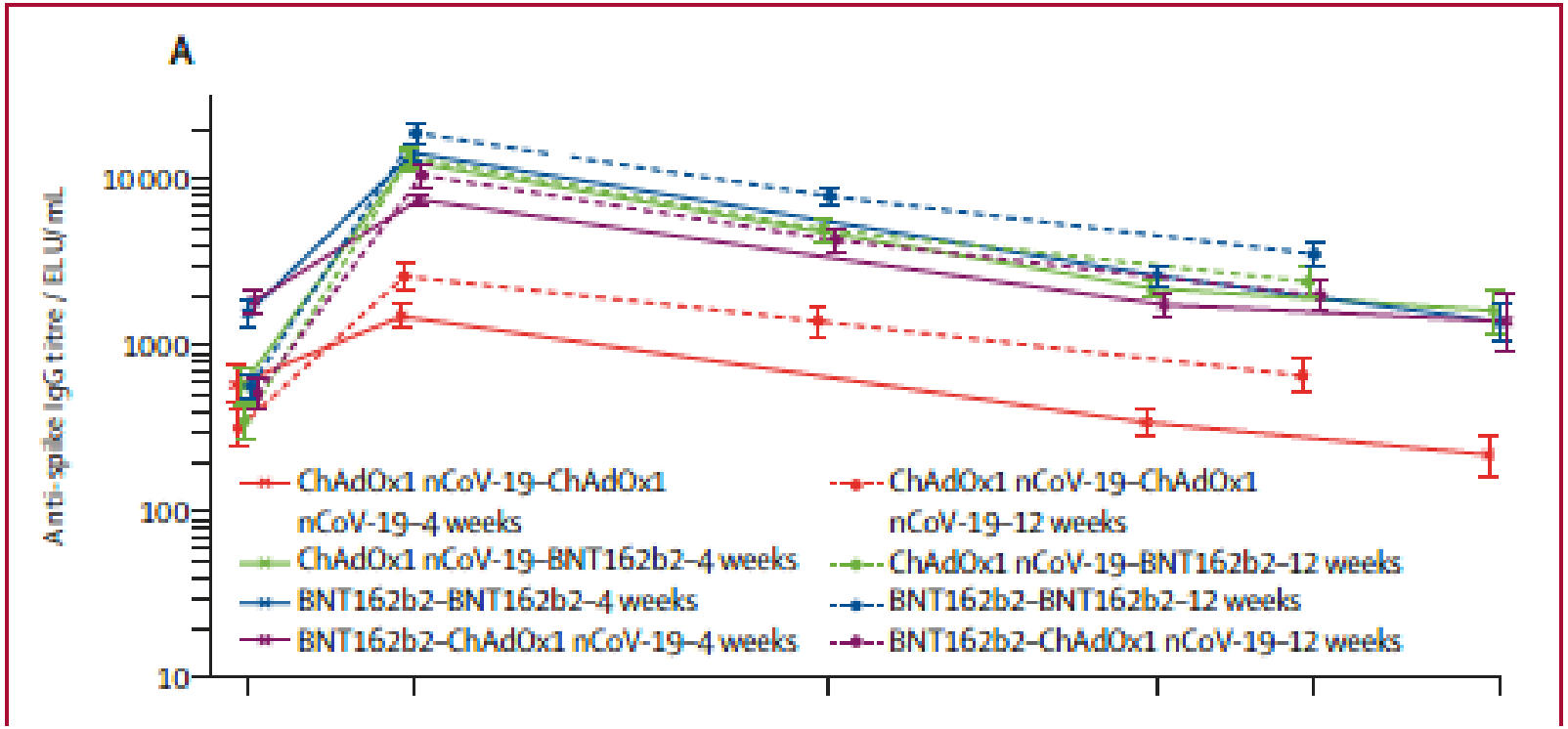
Voysey et al, Clinical and Exp Immunol, 2023

mRNA long interval



Payne et al, Cell 2021

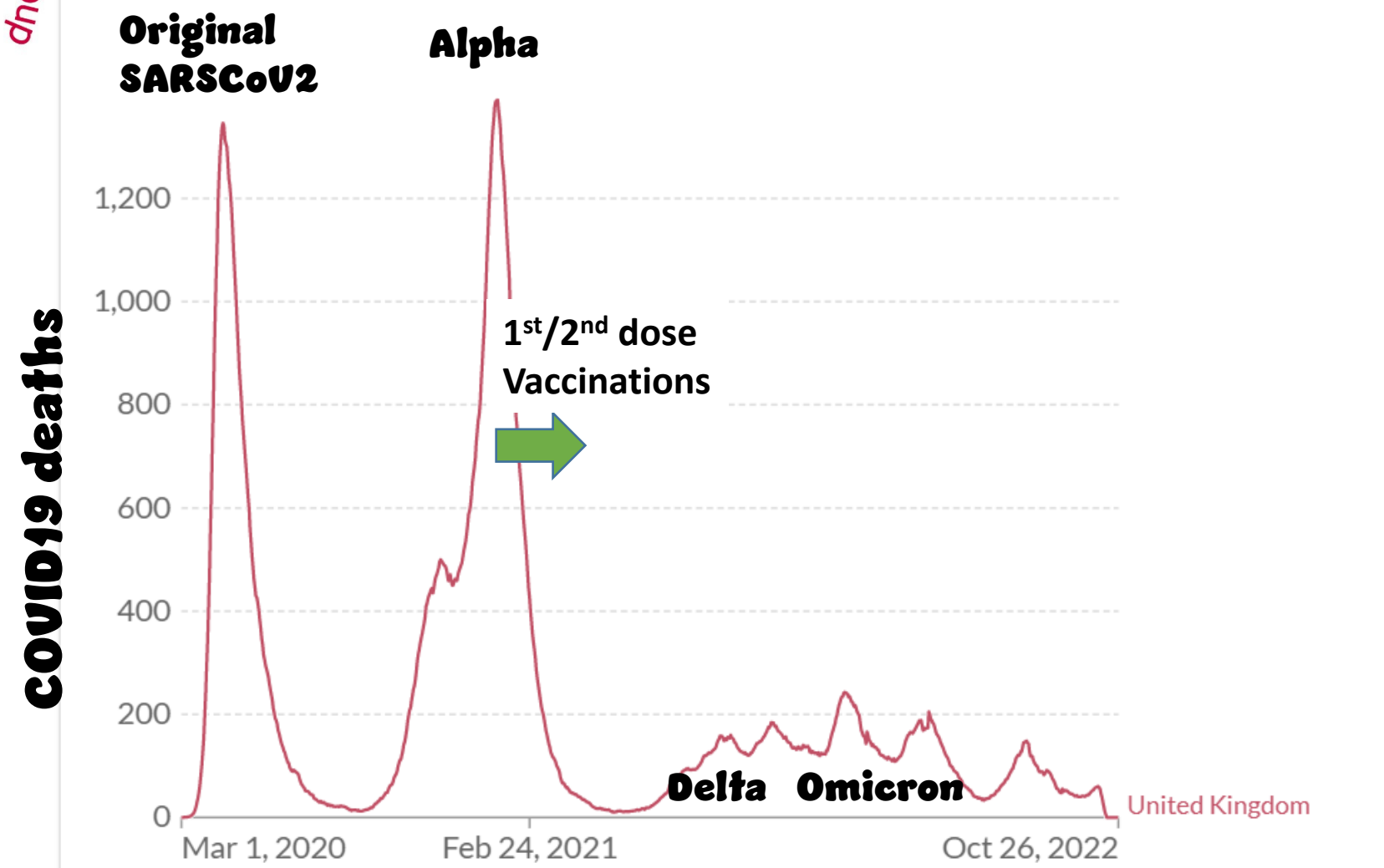
Interval with homologous and heterologous platform



Shaw et al , Lancet Resp Med 2022

Daily new confirmed COVID-19 deaths

7-day rolling average. Due to varying protocols and challenges in the attribution of the cause of death, the number of confirmed deaths may not accurately represent the true number of deaths caused by COVID-19.



Source: Johns Hopkins University CSSE COVID-19 Data

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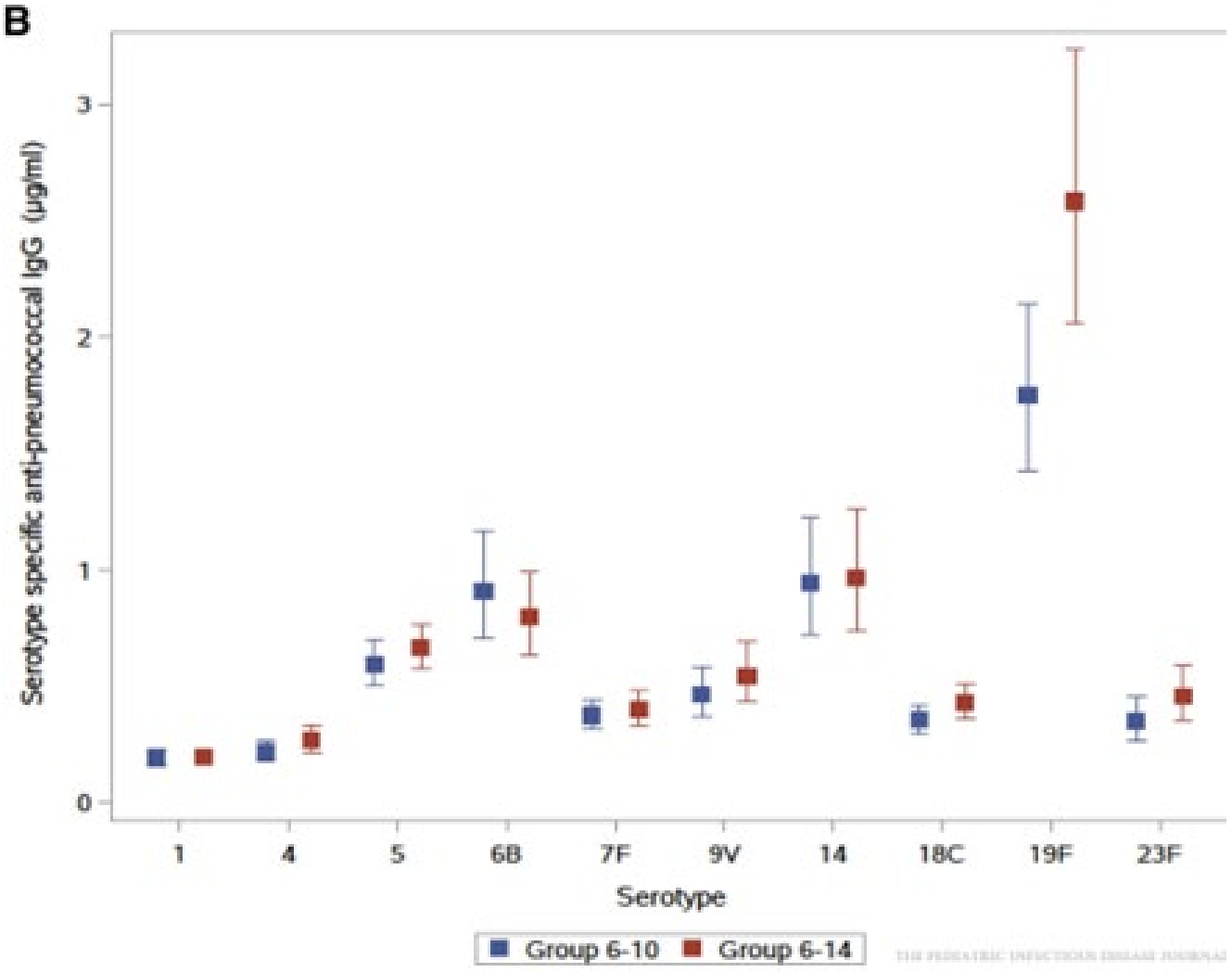
Feb 4, 2020 — Oct 26, 2022

PCV10 at 6/10 or 6/14 weeks



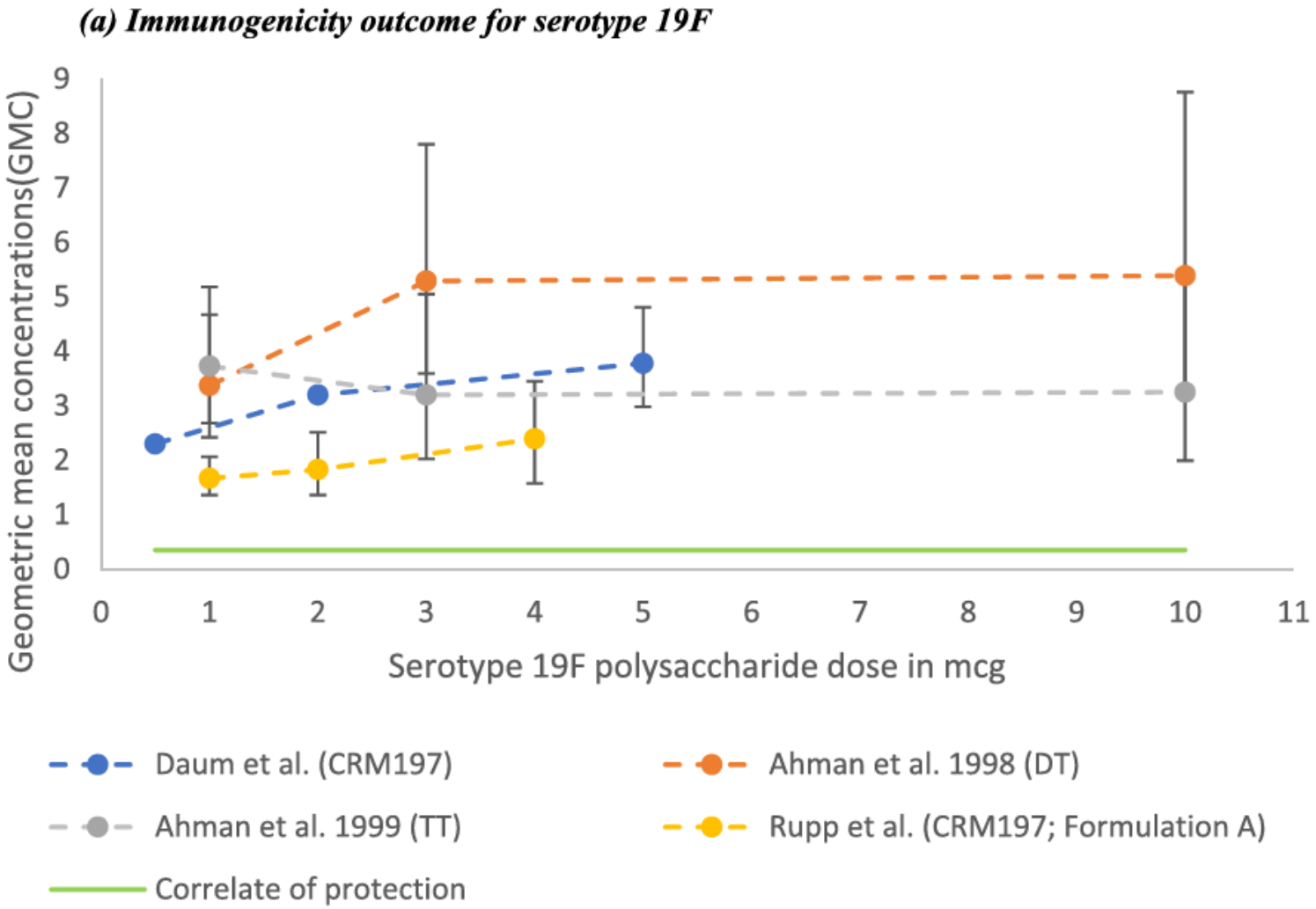
Gurung et al PIDJ, 2021

Interval

- Longer interval = higher antibody response

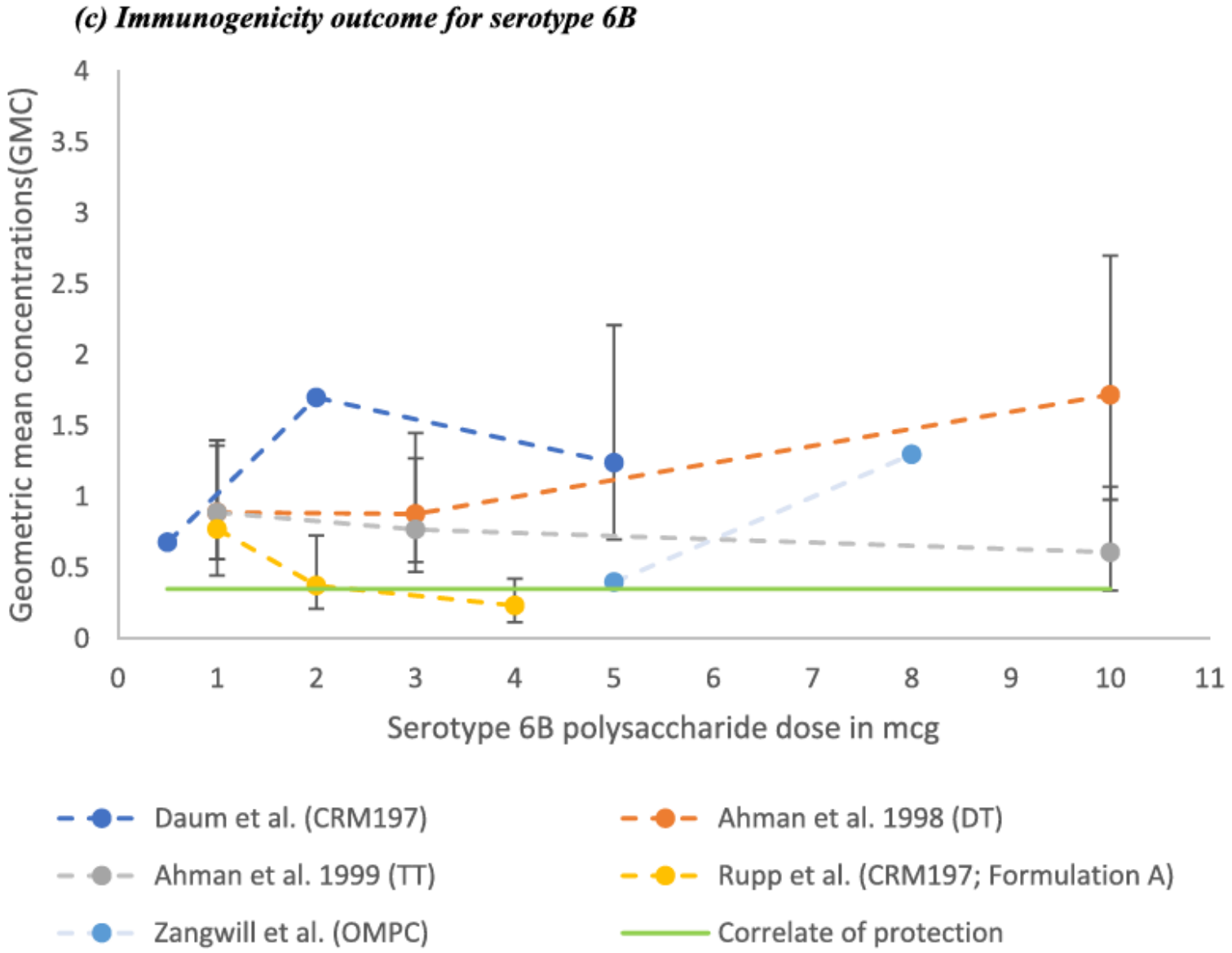
Dose

19F dose response



Lucinde et al, Vaccine 2021

6B dose response



e et al, Vaccine 2021

Hib antibody similar with >1.25mcg

Table 1
Serum PRP antibody concentrations following primary immunization series (18 weeks) and before and after booster dose of vaccine (9 months) with Hib-CRM_{197} conjugate vaccine

Time of measurement of anti-PRP concentrations	0.625 μg (1/16)	1.25 μg (1/8)	2.5 μg (1/4)	5 μg (1/2)	10 μg (Full)
18 Weeks of age					
Number of infants (95% CI)	61	70	57	63	58
%≥0.15 μg/ml	89 (78–94)	100 (95–100)	100 (94–100)	100 (94–100)	98 (91–99)
%≥1.0 μg/ml	67 (55–78)	89 (79–94)	84 (73–91)	79 (68–87)	85 (73–92)
%≥5.0 μg/ml	39 (27–53)	53 (41–65)	49 (36–63)	56 (42–68)	71 (57–82)
Geometric mean anti-PRP concentrations in μg/ml	2.28 (1.38–3.75)	6.33 (4.21–9.50)	5.72 (3.58–9.14)	6.08 (3.95–9.36)	9.79 (6.17–15.53)
9 Months of age (pre-boost)					
Number of infants (95% CI)	25	28	22	29	28
%≥0.15 μg/ml	76 (56–88)	93 (77–98)	91 (72–97)	86 (69–94)	93 (77–98)
%≥1.0 μg/ml	48 (30–66)	68 (49–82)	64 (43–80)	59 (41–74)	75 (57–87)
%≥5.0 μg/ml	12 (3–31)	25 (11–45)	36 (17–59)	17 (6–36)	36 (19–56)
Geometric mean anti-PRP concentrations in μg/ml	0.85 (0.4–1.78)	1.67 (0.88–3.18)	2.35 (0.98–5.6)	1.17 (0.62–2.2)	2.56 (1.32–4.99)
1 Week following 9 month booster					
Number of infants (95% CI)	29	25	22	24	28
%≥0.15 μg/ml	97 (83–99)	100 (87–100)	100 (85–100)	100 (86–100)	100 (88–100)
%≥1.0 μg/ml	90 (74–96)	96 (80–99)	96 (78–99)	92 (74–98)	96 (82–100)
%≥5.0 μg/ml	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Geometric mean anti-PRP concentrations in μg/ml	12.01 (5.28–27.31)	40.45 (19.82–82.55)	37.71 (18.03–78.86)	43.86 (19.8–97.14)	47.47 (30.19–74.62)

Huebner et al, Vaccine 2004

Fractional dose polio, antibody titre (type 2)

Study or subgroup	Two or three doses of fIPV (mean [SD])	Total	Two doses of full-dose IPV (mean [SD])	Total	Weight (%)	SMD (95% CI)
Mohammed et al[29]	6 (4·3)	200	8·1 (3·6)	200	24·7	−0·53 (−0·73 to −0·33)
Resik et al[28]	20 (7·8)	235	130 (199·9)	236	25·3	−0·78 (−0·96 to −0·59)
Resik et al[32]	898 (2371·7)	160	1448 (0·3)	160	23·5	−0·33 (−0·55 to −0·11)
Snider et al[38*]	181 (2073·2)	284	1152 (3634·8)	287	26·5	−0·33 (−0·49 to −0·16)
Total (95% CI)		**879**		**883**	**100·0**	**−0·49 (−0·70 to −0·28)**

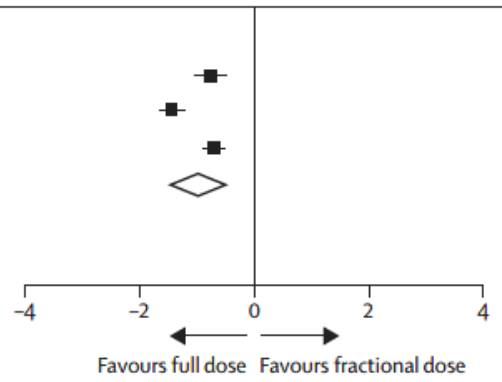
Heterogeneity: τ^2=0·04, χ^2=14·89, df=3 (p=0·002); I^2=80%

Test for overall effect: Z=4·50 (p<0·00001)

Study or subgroup	Three doses of fIPV (mean [SD])	Total	Three doses of full-dose IPV (mean [SD])	Total	Weight (%)	SMD (95% CI)
Cadorna-Carlos et al[30]	233 (299·3)	118	795 (981)	118	32·4	−0·77 (−1·04 to −0·51)
Mohammed et al[29]	8·1 (1·8)	200	10 (0·4)	200	33·4	−1·45 (−1·68 to −1·23)
Resik et al[28]	45 (62·6)	235	214 (325·3)	236	34·1	−0·72 (−0·91 to −0·53)
Total (95% CI)		**553**		**554**	**100·0**	**−0·98 (−1·46 to −0·51)**

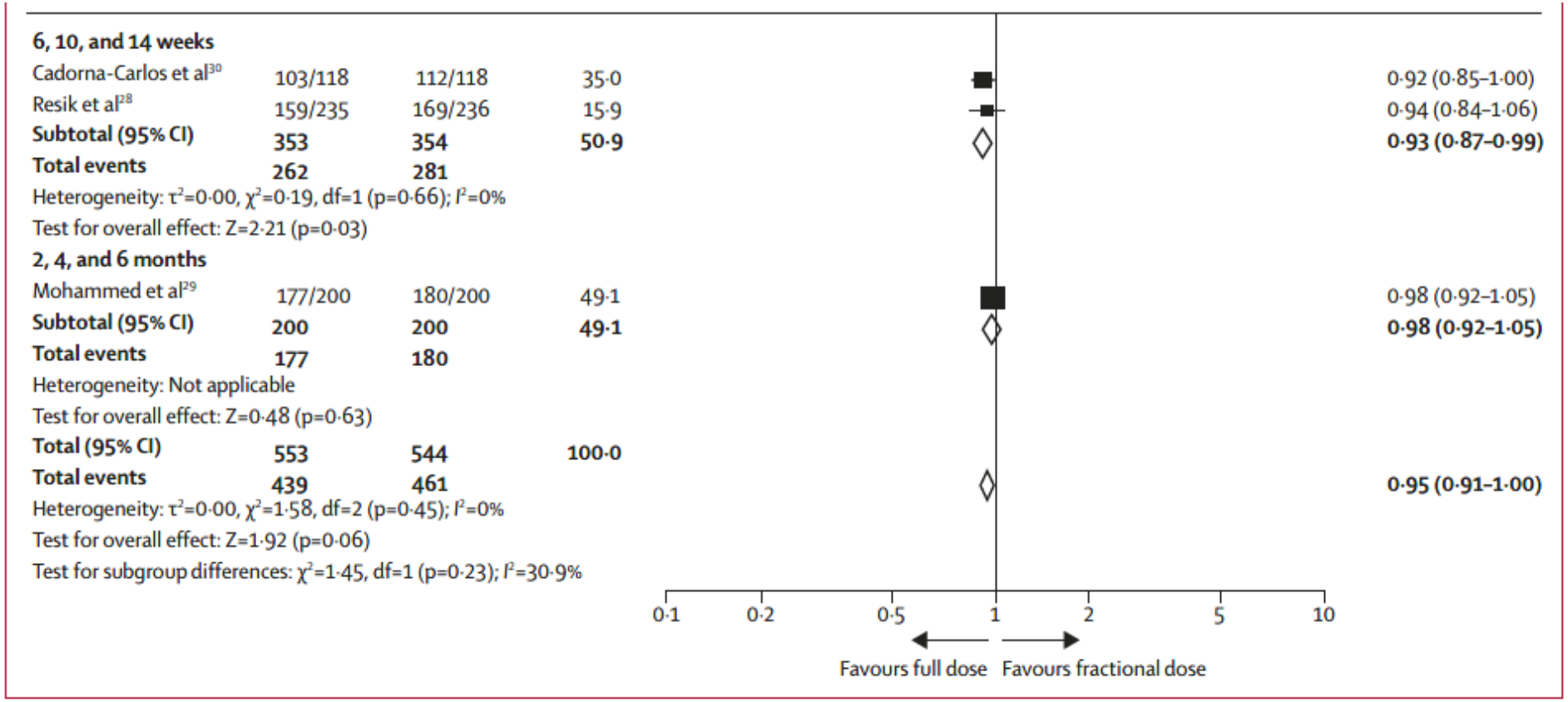
Heterogeneity: τ^2=0·16, χ^2=27·63, df=2 (p<0·00001); I^2=93%

Test for overall effect Z=4·04 (p<0·0001)



Mashunye et al, Lancet ID 2021

Fractional dose polio, seroconversion (type 2)



Mashunye et al, Lancet ID 2021

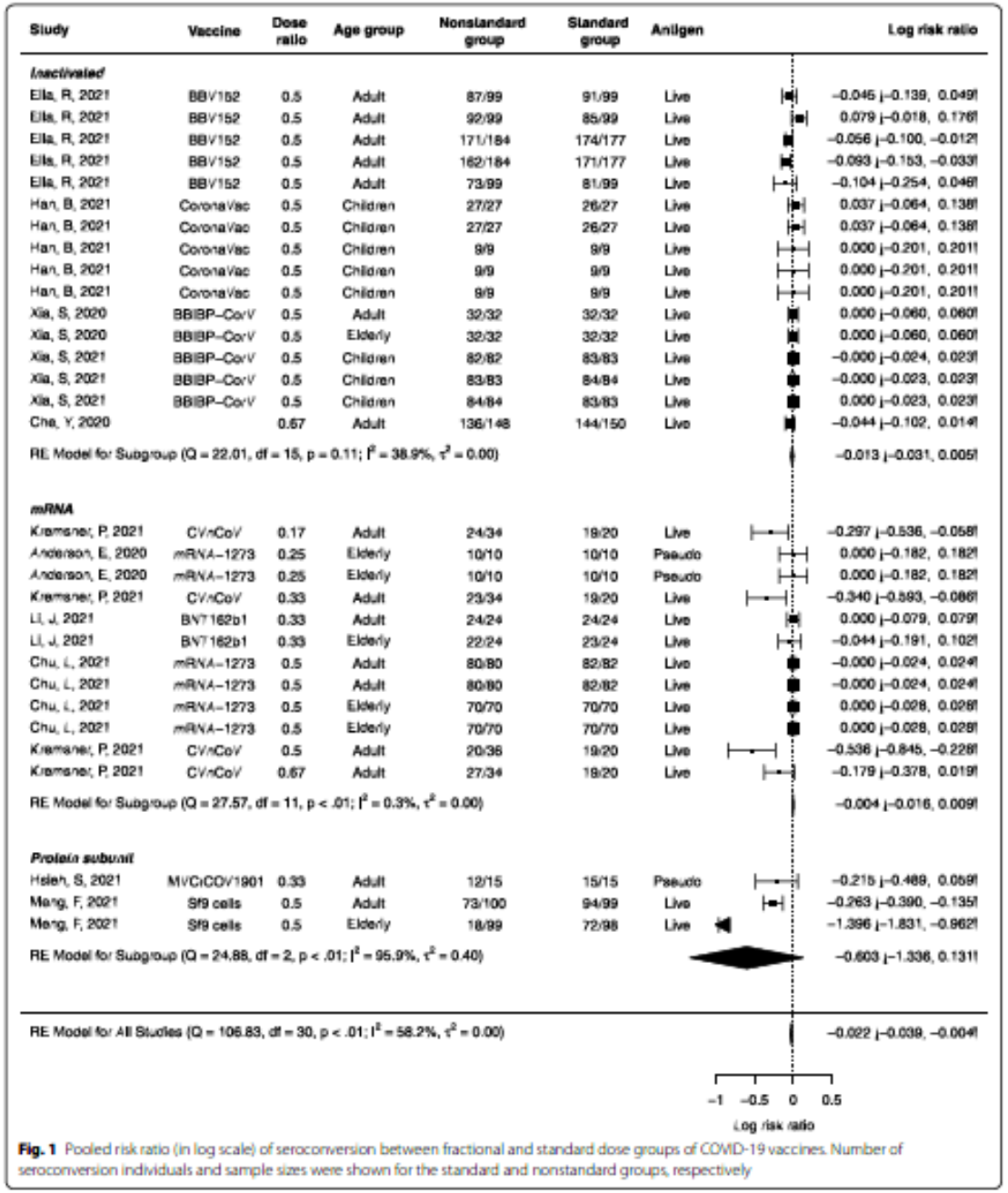


Fig. 1 Pooled risk ratio (in log scale) of seroconversion between fractional and standard dose groups of COVID-19 vaccines. Number of seroconversion individuals and sample sizes were shown for the standard and nonstandard groups, respectively

Fractional dose vs full dose COVID19 vaccines (seroconversion)

Yang et al, BMC Medicine 2022

H5N1

Hemagglutination inhibition (HI) and seroneutralization (SN) antibody response against influenza A/Vietnam/1194/2004 NIBRG-14 (H5N1) on day 42 after two vaccinations on days 0 and 21, by age strata and vaccine group.

	Age strata and vaccine group			
	18–60 years		>60 years	
	30 μg+Ad	7.5 μg	30 μg+Ad	7.5 μg
HI antibody response				
GMT (dil^{-1})	19.4 (15.1; 24.9)	13.0 (10.3; 16.4)	28.9 (22.1; 37.9)	21.4 (16.5; 27.8)
GMTR	4.68 (3.66; 5.97)	3.13 (2.49; 3.93)	5.21 (4.12; 6.59)	3.60 (2.91; 4.46)
Seroprotection rate: *n*/*N*, %	67/146, 45.9% (37.6; 54.3)	50/148, 33.8% (26.2; 42.0)	84/147, 57.1% (48.7; 65.3)	68/149, 45.6% (37.5; 54.0)
Seroconversion or significant titer increase from day 0: *n*/*N*, %	67/146, 45.9% (37.6; 54.3)	49/148, 33.1% (25.6; 41.3)	76/147, 51.7% (43.3; 60.0)	54/148, 36.5% (28.7; 44.8)
SN antibody response				
GMT (dil^{-1})	20.7 (17.9; 23.9)	15.6 (13.8; 17.7)	23.4 (19.6; 27.8)	17.6 (15.0; 20.6)
Fourfold titer rise from day 0: *n*/*N*, %	40/147, 27.2% (20.2; 35.2)	21/148, 14.2% (9.0; 20.9)	32/150, 21.3% (9.0; 20.9)	17/149, 11.4% (6.8; 17.6)

Numbers in parentheses indicate 95% confidence intervals. Numbers in bold indicate results that meet the CHMP HI immunogenicity criteria. GMT: geometric mean titer; GMTR: geometric mean titer ratio.

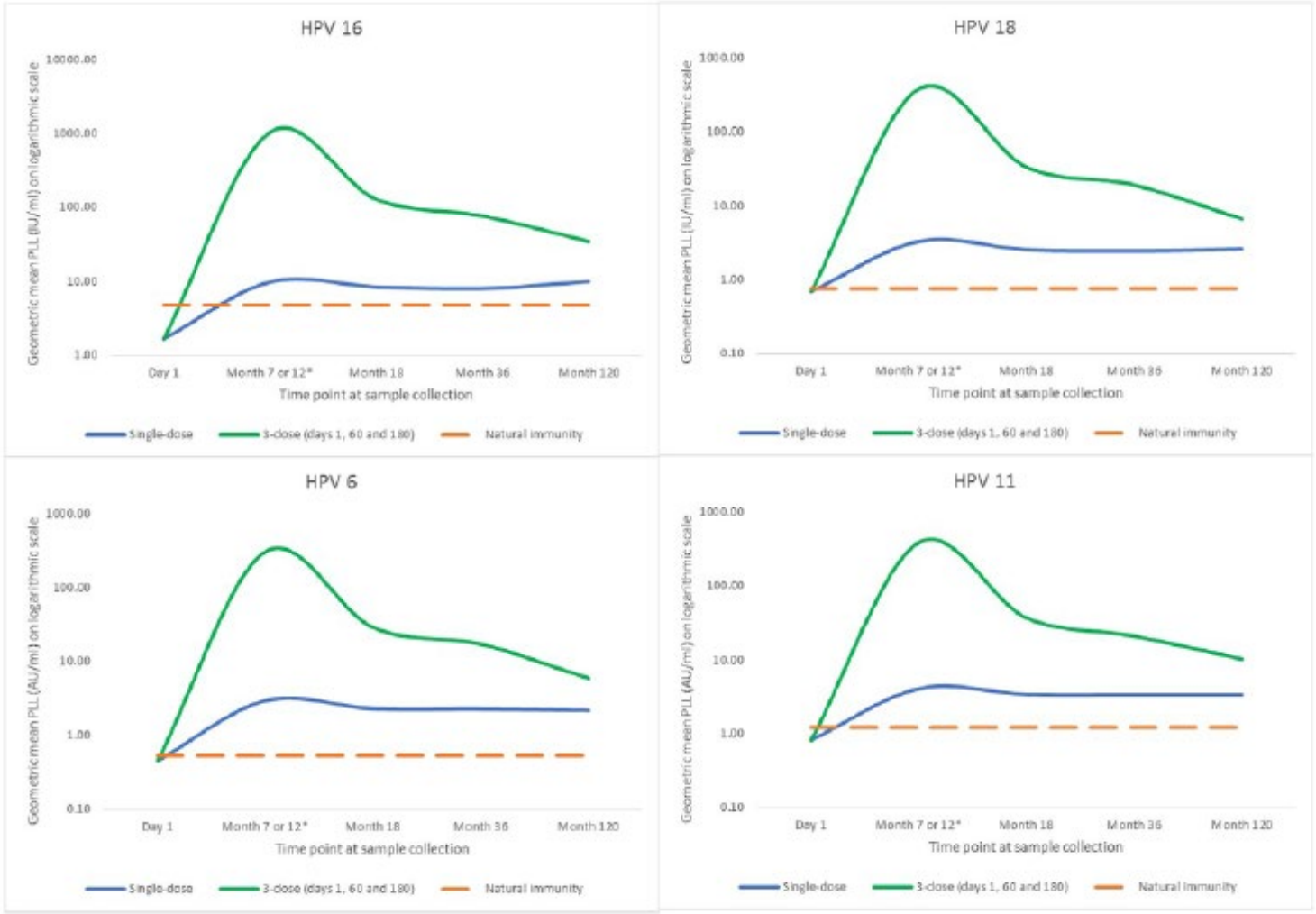
Leroux-Roles et al, Vaccine 2009

Dose

- Higher doses = higher immunogenicity
- But not always
- Seroconversion might be similar across a range of doses
- Clinical significance?

Number of doses

HPV – 3 doses vs 1 dose



Joshi et al, Vaccine 2023

Higher antibody response with more doses of DTP-IPV-Hib

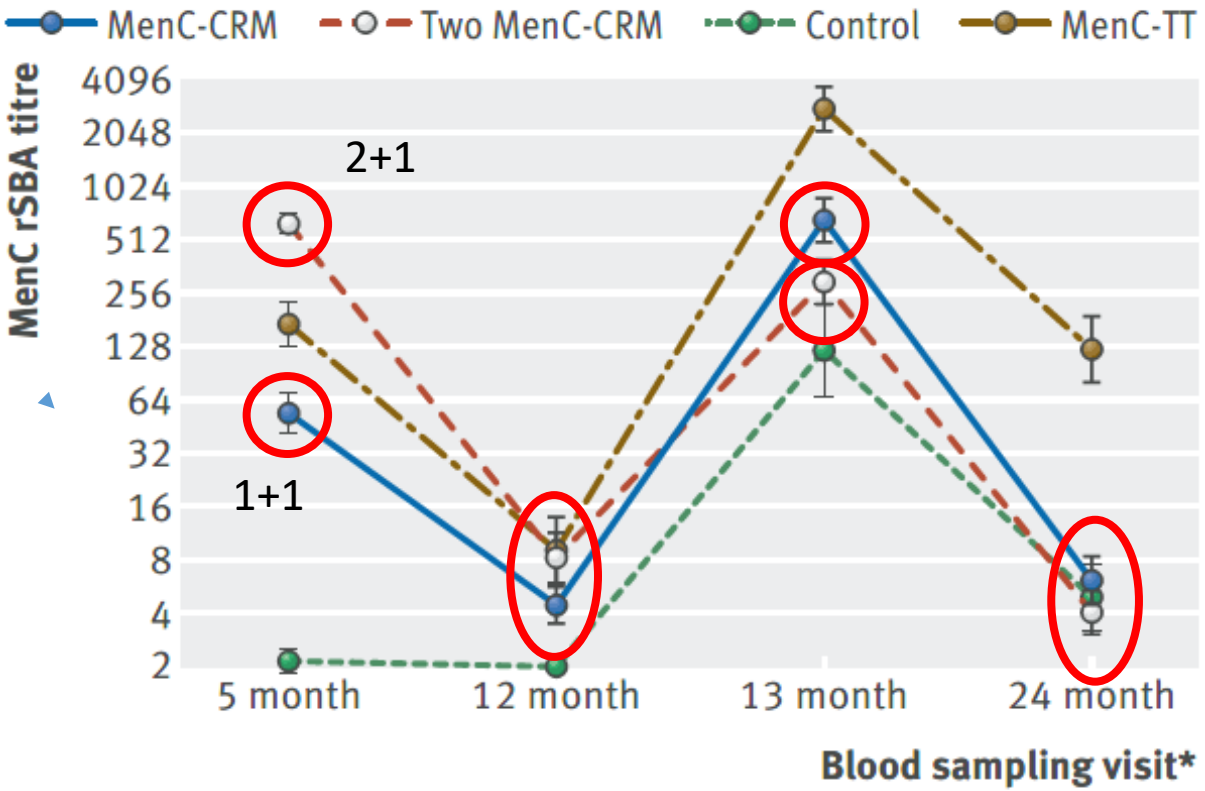
	Serum 1	Serum 2	Serum 3	Serum 4	Serum 5
Diphtheria toxin, IU/ml					
US arm	0.05	0.26**	0.05***	1.9**	0.05*
Swedish arm	0.03	0.38**	0.12***	2.7**	0.09*
Tetanus toxoid, IU/ml					
US arm	0.24	1.7	0.23**	3.5	0.21
Swedish arm	0.27	1.6	0.36**	3.5	0.21
Pertussis toxin, units/ml					
US arm	2.2***	109***	10	154	5.5
Swedish arm	1.1***	81***	14	146	7.2
Hib, µg/ml					
US arm	0.5***	1.9***	1.1**	14.7***	1.5
Swedish arm	0.2***	0.9***	0.6**	8.2***	1.2
Polio type 1, neutralizing titer					
US arm	21**	211**	34***	2002	106
Swedish arm	10**	108**	13***	1490	65
Polio type 2, neutralizing titer					
US arm	Not done	Not done	Not done	Not done	243**
Swedish arm	Not done	Not done	Not done	Not done	110**
Polio type 3, neutralizing titer					
US arm	17***	326	41***	2421	76*
Swedish arm	6***	218	15***	1727	40*

Higher antibody response with more doses, higher doses and longer interval

2,4,6,15 vs 3,5,12 months

Taranger et al, Vaccine 2000

MenC – 2 doses better than 1 dose but no difference by a year of age after a booster



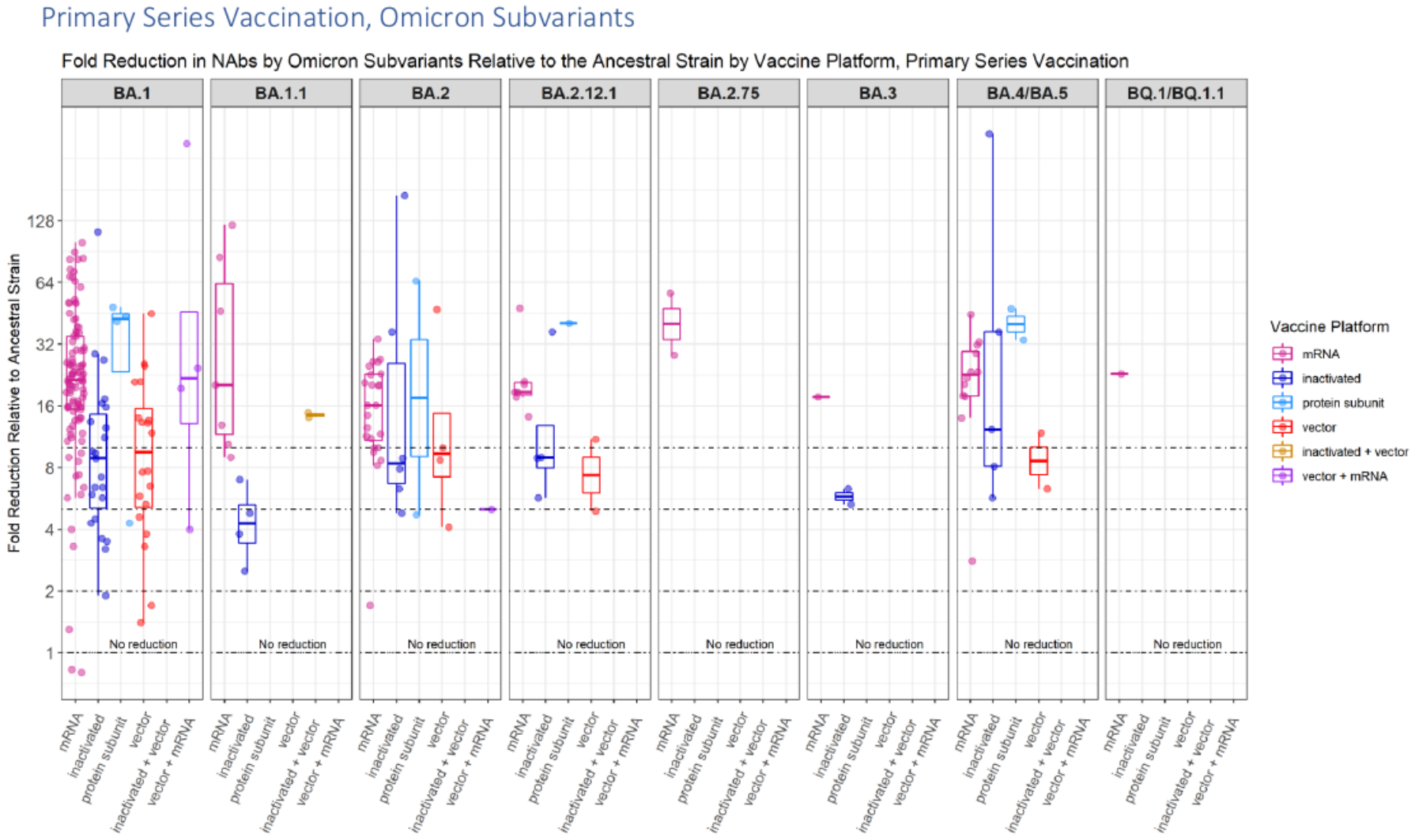
*5 month visit: 28-42 days after last vaccinations administered at 4 months of age; 12 month visit: at 51-58 weeks of age; 13 month visit: 28-42 days after Hib-MenC-TT vaccination at 51-58 weeks of age; 24 month visit: 11-12 months after Hib-MenC-TT vaccination

Pace et al BMJ, 2015

Platform

Platform differences

Antigen
Platform?
Dose?
Adjuvant?

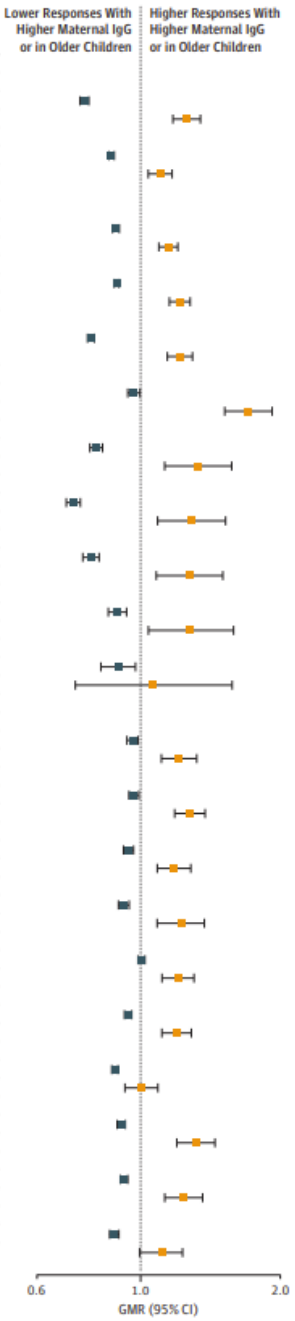


Hopkins, View hub

Older age and lower maternal antibody associated with stronger immune response

Figure 1. Influence of Age at First Vaccination and Preexisting Antibody Concentration Prior to Vaccination on Antibody Concentration After the Third Priming Dose

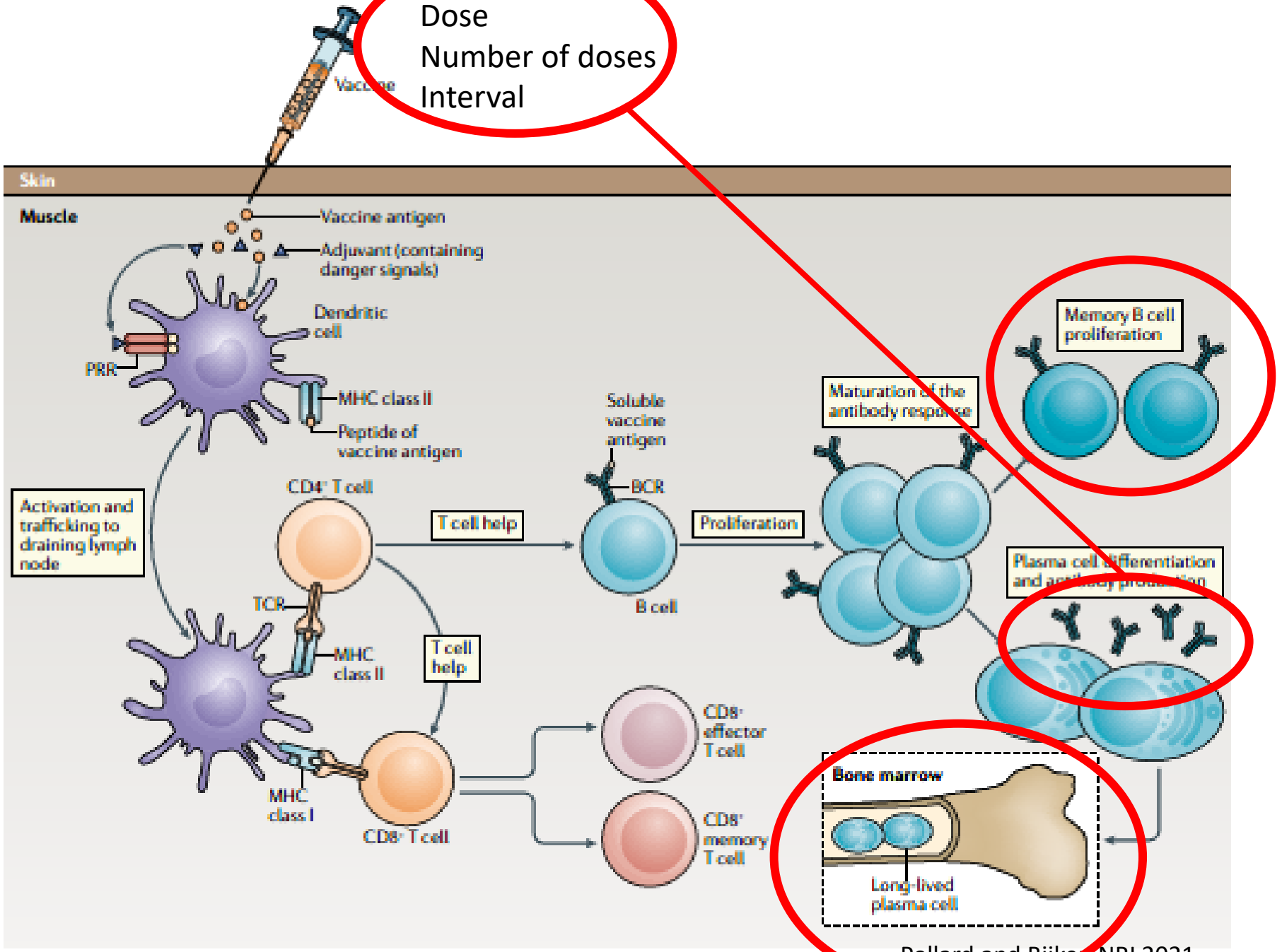
Source	No. of Participants	GMR (95% CI)
Antigen		
Diphtheria	4897	
Maternal IgG (per 2-fold increase)		0.76 (0.74-0.77)
Age at first vaccination (per month older)		1.26 (1.18-1.35)
Tetanus	4188	
Maternal IgG (per 2-fold increase)		0.87 (0.86-0.88)
Age at first vaccination (per month older)		1.10 (1.04-1.17)
Pertussis		
PT	4941	
Maternal IgG (per 2-fold increase)		0.89 (0.87-0.90)
Age at first vaccination (per month older)		1.15 (1.10-1.20)
FHA	4952	
Maternal IgG (per 2-fold increase)		0.89 (0.88-0.90)
Age at first vaccination (per month older)		1.22 (1.16-1.28)
PRN	4778	
Maternal IgG (per 2-fold increase)		0.78 (0.77-0.80)
Age at first vaccination (per month older)		1.22 (1.14-1.29)
PRP	3369	
Maternal IgG (per 2-fold increase)		0.97 (0.94-1.00)
Age at first vaccination (per month older)		1.71 (1.52-1.92)
Polio 1	1699	
Maternal IgG (per 2-fold increase)		0.80 (0.78-0.83)
Age at first vaccination (per month older)		1.33 (1.13-1.57)
Polio 2	1699	
Maternal IgG (per 2-fold increase)		0.72 (0.69-0.74)
Age at first vaccination (per month older)		1.29 (1.09-1.53)
Polio 3	1699	
Maternal IgG (per 2-fold increase)		0.78 (0.75-0.82)
Age at first vaccination (per month older)		1.28 (1.08-1.51)
Hepatitis B	1180	
Maternal IgG (per 2-fold increase)		0.89 (0.85-0.94)
Age at first vaccination (per month older)		1.28 (1.04-1.59)
Group C meningococcus	1082	
Maternal IgG (per 2-fold increase)		0.90 (0.82-0.98)
Age at first vaccination (per month older)		1.07 (0.73-1.58)
Serotype		
1	2387	
Maternal IgG (per 2-fold increase)		0.96 (0.94-0.99)
Age at first vaccination (per month older)		1.21 (1.11-1.32)
4	3057	
Maternal IgG (per 2-fold increase)		0.97 (0.95-0.99)
Age at first vaccination (per month older)		1.28 (1.19-1.38)
5	2387	
Maternal IgG (per 2-fold increase)		0.94 (0.92-0.97)
Age at first vaccination (per month older)		1.18 (1.08-1.28)
6B	3057	
Maternal IgG (per 2-fold increase)		0.92 (0.90-0.95)
Age at first vaccination (per month older)		1.22 (1.09-1.37)
7F	2387	
Maternal IgG (per 2-fold increase)		1.01 (0.99-1.02)
Age at first vaccination (per month older)		1.21 (1.11-1.31)
9V	3057	
Maternal IgG (per 2-fold increase)		0.94 (0.93-0.96)
Age at first vaccination (per month older)		1.20 (1.11-1.29)
14	3057	
Maternal IgG (per 2-fold increase)		0.88 (0.87-0.90)
Age at first vaccination (per month older)		1.01 (0.93-1.09)
18C	3057	
Maternal IgG (per 2-fold increase)		0.91 (0.89-0.93)
Age at first vaccination (per month older)		1.32 (1.20-1.45)
19F	3057	
Maternal IgG (per 2-fold increase)		0.92 (0.91-0.94)
Age at first vaccination (per month older)		1.24 (1.13-1.36)
23F	3057	
Maternal IgG (per 2-fold increase)		0.88 (0.86-0.90)
Age at first vaccination (per month older)		1.11 (1.00-1.23)



The Influence of Maternally Derived Antibody and Infant Age at Vaccination on Infant Vaccine Responses An Individual Participant Meta-analysis

Voysey et al, JAMA Paediatrics, 2017

Dose
Number of doses
Interval



Pollard and Bijker, NRI 2021

Summary

- Higher doses generally better response
  - But costs more to make
  - Might be more reactogenic
  - Aim for lowest dose that works
- More doses generally better response
  - Increased costs for more visits/doses
  - Decreased compliance
- Longer interval better response
  - But longer period of risk between doses
  - Later dosing decreased compliance

- Clinical significance of the higher responses for important endpoints often uncertain
- Immunology is a work in progress

Group/ schedule	6 weeks	8 weeks (2 months)	10 weeks	12 weeks (3 months)	14 weeks	16 weeks (4 months)	18 weeks	20 weeks	24 weeks (6 months)	28 weeks (7 months)	*9 months*	*10 months*	*12 months*	*13 months*	*18 months*	2 years
1: "WHO" 6, 10, 14 weeks N=212	DTwP-Hib-HBV + PCV + rota + bOPV Blood 1a N=70		DTwP-Hib-HBV + rota + bOPV Blood 1b N=71		DTwP-Hib-HBV + PCV + bOPV +IPV Blood 1c N=71		Blood 2 N=212				MR + PCV + DTwP-Hib-HBV Blood 3 N=106	TCV+YF Blood 4a N=53			MR	Varicella Blood 4b N=106
											MR + PCV + YF/TCV	+ YF/TCV	DTwP-Hib-HBV Blood 3 N=106	Blood 4a N=53	MR	
2 : "Modified EPI" 6, 14 weeks N=212	DTwP-Hib-HBV + PCV + rota + bOPV Blood 1a N=70		bOPV Blood 1b N=71		DTwP-Hib-HBV + PCV + rota + bOPV +IPV Blood 1c N=71		Blood 2 N=212				MR + PCV + DTwP-Hib-HBV Blood 3 N=106	TCV+YF Blood 4a N=53			MR	Varicella Blood 4b N=106
											MR + PCV + YF/TCV	+ YF/TCV	DTwP-Hib-HBV Blood 3 N=106	Blood 4a N=53	MR	
3: "Optimms" 2, 4 months N=212	Consent/ Randomisation visit	DTwP-Hib-HBV + PCV + rota + bOPV Blood 1a N=106				DTwP-Hib-HBV + PCV + rota + bOPV +IPV Blood 1c N=106		bOPV Blood 2 N=212			MR + PCV + DTwP-Hib-HBV Blood 3 N=106	TCV+YF Blood 4a N=53			MR	Varicella Blood 4b N=106
											MR + PCV + YF/TCV	+ YF/TCV	DTwP-Hib-HBV Blood 3 N=106	Blood 4a N=53	MR	
4: "2-3-4" 2, 3, 4 months N=160	Consent/ Randomisation visit	DTwP-Hib-HBV + PCV + rota + bOPV		DTwP-Hib-HBV + rota + bOPV Blood 1b N=80		DTwP-Hib-HBV + PCV + bOPV +IPV Blood 1c N=80		Blood 2 N=160			MR + PCV + DTwP-Hib-HBV Blood 3 N=80	TCV+YF Blood 4a N=40			MR	Varicella Blood 4b N=80
											MR + PCV + YF/TCV	+ YF/TCV	DTwP-Hib-HBV Blood 3 N=80	Blood 4a N=40	MR	
5: "2-4-6" 2, 4, 6 months N=160	Consent/ Randomisation visit	DTwP-Hib-HBV + PCV + rota + bOPV Blood 1a N=80				DTwP-Hib-HBV + PCV + rota + bOPV +IPV			DTwP-Hib-HBV + bOPV Blood 1c N=80	Blood 2 N=160	MR + PCV + YF/TCV	+ YF/TCV	DTwP-Hib-HBV Blood 3 N=160	Blood 4a N=80	MR	Varicella Blood 4b N=80

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