Is Immunological Tolerance a Real Concern?

William Moss

Question

Does vaccination below 9 months result in immunological tolerance (unresponsiveness to subsequent doses)?

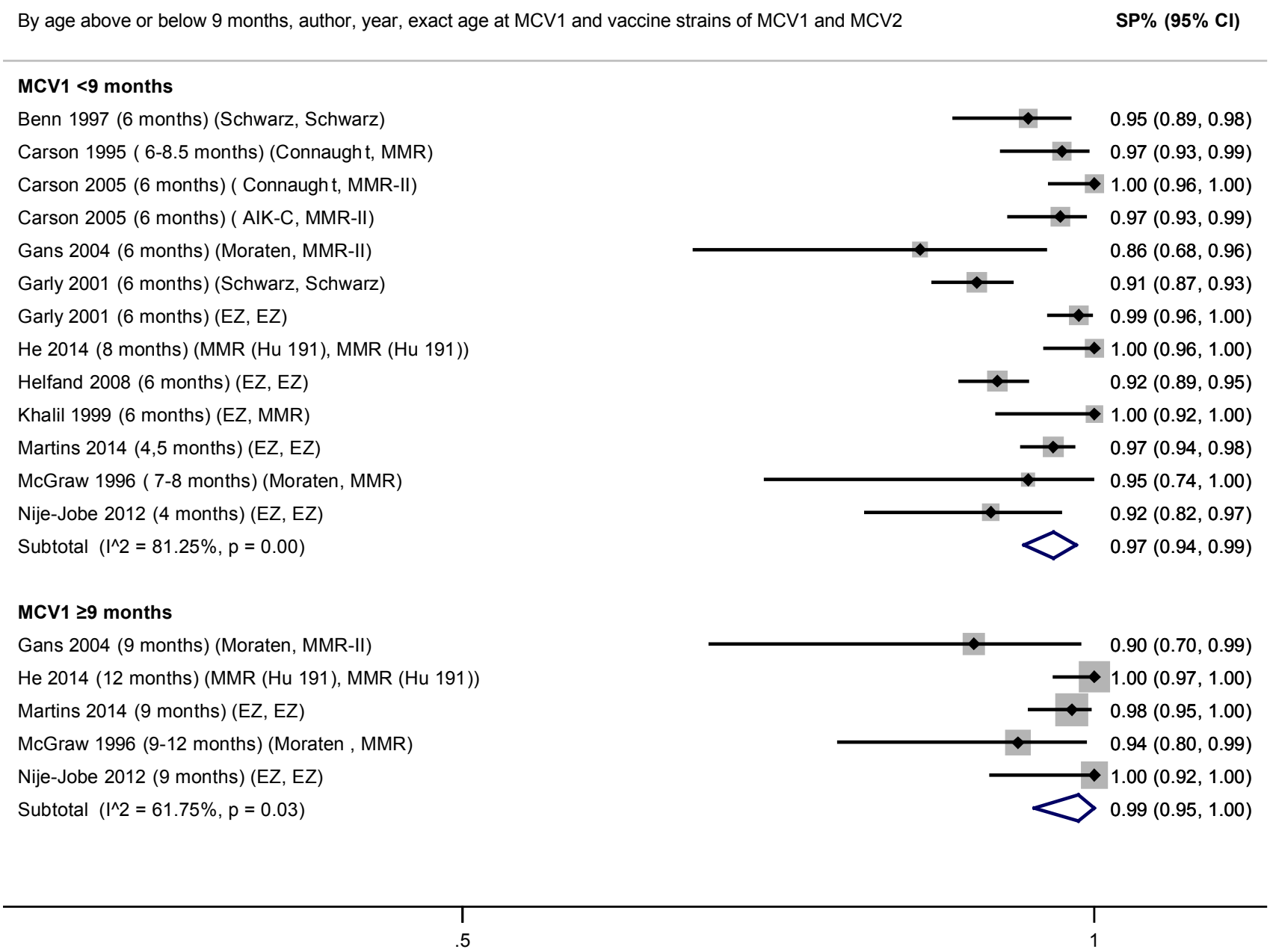
Immunological Tolerance

Immunological tolerance is the non-reactivity of the immune system to an antigen as a consequence of specific immunologic mechanisms, most importantly to self antigens.

Hyporesponsiveness following vaccination has been best described with meningococcal and pneumococcal polysaccharide vaccines.

Blunting of Immune Responses Due to Pre-Existing Immunity

Immunological tolerance is to be distinguished from impaired or blunted immune responses to attenuated viral vaccines due to the presence of pre-existing neutralizing antibodies.


By age above or below 9 months, author, year, exact age at MCV1 and vaccine strains of MCV1 and MCV2
SP% (95% CI)
MCV1 <9 months
Benn 1997 (6 months) (Schwarz, Schwarz)
0.95 (0.89, 0.98)
Carson 1995 (6-8.5 months) (Connaught, MMR)
0.97 (0.93, 0.99)
Carson 2005 (6 months) (Connaught, MMR-II)
1.00 (0.96, 1.00)
Carson 2005 (6 months) (AIK-C, MMR-II)
0.97 (0.93, 0.99)
Gans 2004 (6 months) (Moraten, MMR-II)
0.86 (0.68, 0.96)
Garly 2001 (6 months) (Schwarz, Schwarz)
0.91 (0.87, 0.93)
Garly 2001 (6 months) (EZ, EZ)
0.99 (0.96, 1.00)
He 2014 (8 months) (MMR (Hu 191), MMR (Hu 191))
1.00 (0.96, 1.00)
Helfand 2008 (6 months) (EZ, EZ)
0.92 (0.89, 0.95)
Khalil 1999 (6 months) (EZ, MMR)
1.00 (0.92, 1.00)
Martins 2014 (4,5 months) (EZ, EZ)
0.97 (0.94, 0.98)
McGraw 1996 (7-8 months) (Moraten, MMR)
0.95 (0.74, 1.00)
Nije-Jobe 2012 (4 months) (EZ, EZ)
0.92 (0.82, 0.97)
Subtotal (I^2 = 81.25%, p = 0.00)
0.97 (0.94, 0.99)
MCV1 ≥9 months
Gans 2004 (9 months) (Moraten, MMR-II)
0.90 (0.70, 0.99)
He 2014 (12 months) (MMR (Hu 191), MMR (Hu 191))
1.00 (0.97, 1.00)
Martins 2014 (9 months) (EZ, EZ)
0.98 (0.95, 1.00)
McGraw 1996 (9-12 months) (Moraten , MMR)
0.94 (0.80, 0.99)
Nije-Jobe 2012 (9 months) (EZ, EZ)
1.00 (0.92, 1.00)
Subtotal (I^2 = 61.75%, p = 0.03)
0.99 (0.95, 1.00)
.5
1

Early Reviews

Black FL. **Measles active and passive immunity in a worldwide perspective**. Prog Med Virol. 1989;36:1-33.

”Premature vaccination not only fails to immunize, but also interferes with subsequent re-immunization..”

Rosenthal SR, Clements CJ. **Two-dose measles vaccination schedules**. Bull World Health Organ. 1993;71:421-8.

“ Several studies suggest that those infants who received measles immunization early in life have a lower antibody response to a subsequent dose of measles vaccine than those who were first immunized after the age of 12 months.”

Two-Dose Schedule with MCV1 ≤ 9 Months
History of Concerns and Responses

First Author	Year	Country	Age at 1st dose	Age at 2nd dose	Sero-positive 1	Sero-positive 2	
Wilkins	1979	US	6-10	>12	NA	49	37 “vaccine failures” by HI; all neutralizing antibodies
			>12	-	93		
Linnemann	1982	US	<10	>12	NA	60	GMT by HI lower if MCV1 <7
Black	1984	Brazil	5-12	>24	54	60	79 vaccine failures by HI; good 1° response to MCV2 but waned; wt-MV present
Murphy	1984	US	5-10	>15	NA	98	ELISA not HI; change in OD lower with revaccination (0.38 vs. 0.51)
			>15	-	98		
McGraw	1986	US	7-12	15-18	89	94	Included in RIVM review
			15-18	-	95		
Stetler	1986	US	<10	>15	48	96	Lower HI and EIA at 8 months but not neutralizing Abs
			15-23	-	99		

3 Weeks Post Vaccination

TABLE 1. Antibody Test Results of Study and Control Infants 3 Weeks Following Revaccination or Primary Vaccination*

Antibody Test	Study Infants	Control Infants	*P* Value
HI	29.53 (121)	22.69 (127)	<.005
CPEN	156.90 (120)	276.65 (126)	<.001
ELISA	0.456 (102)	0.266 (107)	<.001

* Results are geometric mean titers by hemagglutination inhibition (HI) and cytopathic effect neutralization (CPEN) tests and mean optical density values by enzyme-linked immunoassay (ELISA) of initially HI-negative infants. Numbers in parentheses are numbers of blood specimens tested. Probability was determined by Student's *t* test.

Stetler HC, Orenstein WA, Bernier RH, Herrmann KL, Sirotkin B, Hopfensperger D, Schuh R, Albrecht P, Lievens AW, Brunell PA. Impact of revaccinating children who initially received measles vaccine before 10 months of age. Pediatrics. 1986;77:471-6.

8 Months Post Vaccination

TABLE 4. Comparison of All Infants With Detectable Antibody Titers at 8 Months Following Revaccination (Study Infants) or Primary Vaccination (Control Infants)*

Assay	Study Infants	Control Infants	*P* Value
HI ≥ 1:8	76.4 (254)	97.7 (129)	<.001
CPEN ≥ 1:4	98.4 (253)	99.2 (129)	.903
ELISA ≥ 0.056	92.3 (234)	99.2 (118)	<.008
HI ≥ 1:8 or CPEN ≥ 1:4 or ELISA ≥ 0.056	98.4 (253)	99.2 (129)	.903

* Abbreviations used are; HI, hemagglutination inhibition; CPEN, cytopathic effect neutralization; ELISA, enzyme-linked immunoassay. Numbers of blood specimens tested are given in parentheses. Probability was tested by Fisher exact two-tailed test.

Differences are assay dependent and correlations with protective immunity unclear

Stetler HC, Orenstein WA, Bernier RH, Herrmann KL, Sirotkin B, Hopfensperger D, Schuh R, Albrecht P, Lievens AW, Brunell PA. Impact of revaccinating children who initially received measles vaccine before 10 months of age. Pediatrics. 1986;77:471-6.

Potential Waning Immunity

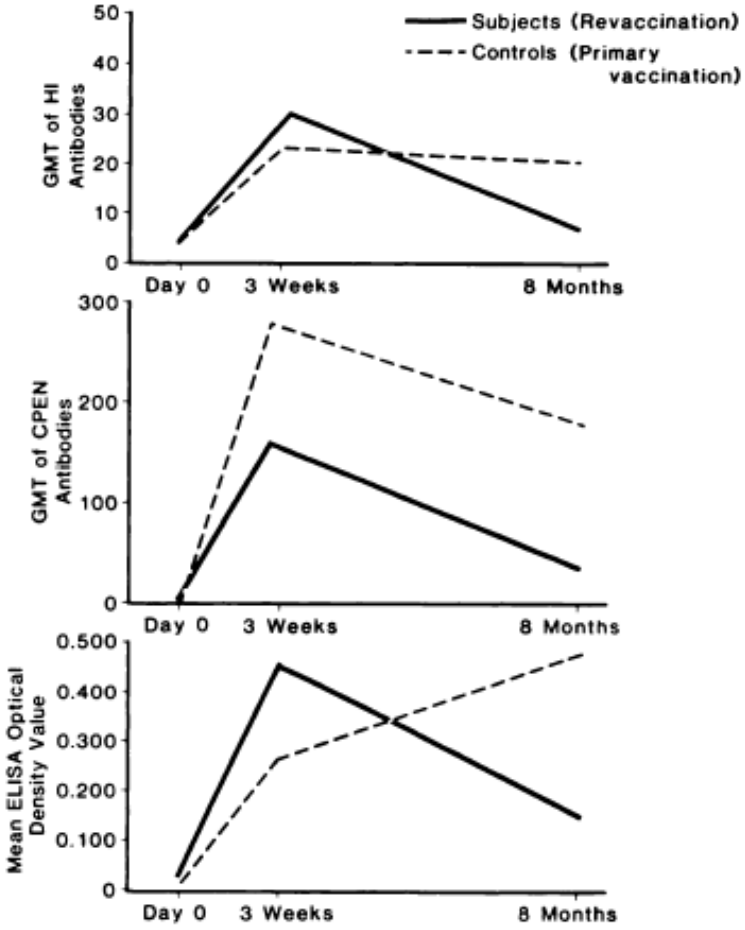


Fig 2. Geometric mean titers (GMT) of hemagglutination inhibition (HI) and cytopathic effect neutralization (CPEN) antibodies and mean enzyme-linked immunoassay (ELISA) optical density values. Results are shown for infants whose first blood specimens were negative for HI antibodies.

Waning antibody concentrations after early two-dose schedule could explain discrepancies between HI and PNR assay results

Stetler HC, Orenstein WA, Bernier RH, Herrmann KL, Sirotkin B, Hopfensperger D, Schuh R, Albrecht P, Lievens AW, Brunell PA. Impact of revaccinating children who initially received measles vaccine before 10 months of age. Pediatrics. 1986;77:471-6.

Additional Studies Not in RIVM Review

First Author	Year	Country	MCV1	MCV2	Age at 1st dose	Age at 2nd dose	Sero-positive 1	Sero-positive 2	
Pannuti	1990	Brazil	BC	BC	6	11	NA	97	ELISA 6-12 months after MCV2
Schnorr	2001	Bangladesh	EZ/Sw	EZ/Sw	6	9	56	91	>200 mIU/mL by PRN; GMT lower with early dose (465 vs. 509); cellular immune responses similar
			EZ/Sw		9		95		
Hutchins	2001	US			6-11	12-18		88	EIA, MN and PRN >3 years after MCV2; GMT lower with early dose (999 vs. 1440)
					12-18		97		
Fowlkes	2011	Malawi	EZ	EZ	6	9		87	Follow-up of Helfand to 24 months
			EZ		9	-	84	-	

RIVM Review Studies with Comparison Groups

First Author	Year	Country	MCV1	MCV2	Age at 1st dose	Age at 2nd dose	Sero-positive 1	Sero-positive 2	Comments
Benn	1997	GB	SW	SW	6	9	70	95	Vitamin A trial; HI
			SW		9	-	95	-	
Garly	2001	GB	EZ		6	9	95	99	HI; GMT lower for SW early two-dose but similar for EZ
					9		99	-	
Garly	2001	GB	SW		6	9	78	91	
					9		97	-	
Gans	2004	US	M	MMR	6	12	52	86	PRN; GMT lower in absence of passive Abs after early two-dose
			M		9	12	90	90	
			MMR		-	12	96	-	
Helfand	2008	Malawi			6	9	62	92	EIA at 12 months
					9	-	76	-	
Nije-Jobe	2012	Gambia	EZ	EZ	4	9	66	98	HI at 2-weeks; lower Ab at 18 months; cellular immunity similar
			EZ		9	-	36	-	
Martins	2014		EZ	EZ	4.5	9	77	97	GMT lower in early two-dose group
			EZ		9	-	99	-	
He	2014	China	MMR	MMR	8	18	100	100	GMT by EIA not different after MCV2
			MMR	MMR	12	22	100	100	

Early Two Dose (6+9) vs. 9 Months

Geometric mean measles antibody titre (mIU/ml), and percent unprotected children according to age, number of doses and measles vaccine strain[a]

		One dose of measles vaccine at 6 months of age		One dose of measles vaccine at 9 months of age		Two doses of measles vaccine at 6 and 9 months of age	
		GMT (95% CI) at 9 months of age	Percent unprotected at 9 months of age	GMT (95% CI) at 18 months of age	Percent unprotected at 18 months of age	GMT (95% CI) at 18 months of age	Percent unprotected at 18 months of age
EZ measles vaccine		1174 (962–1433)	4.9%	1525 (1349–1723)	1.4%	1569 (1385–1780)	1.3%
	n	77	4/81	208	3/211	236	3/239
SW measles vaccine		1338 (1055–1697)	21.7%	2491 (2231–2781)	2.9%	1125 (994–1273)	9.3%
	n	83	23/106	301	9/310	331	34/365

[a] GMT, geometric mean titre (mIU/ml); CI, confidence interval; SW, standard-titre Schwarz measles vaccine; EZ, standard-titre Edmonston-Zagreb measles vaccine.

Vaccine strain important in assessing early two-dose schedule

Garly ML, Balé C, Martins CL, Monteiro M, George E, Kidd M, Dias F, Aaby P, Whittle HC. Measles antibody responses after early two dose trials in Guinea-Bissau with Edmonston-Zagreb and Schwarz standard-titre measles vaccine: better antibody increase from booster dose of the Edmonston-Zagreb vaccine. Vaccine. 2001;19:1951-9.

Early Two Dose (6+12) vs. 9+12 Months

Table 1. Humoral immune responses to 1 dose and 2 doses of measles vaccine.

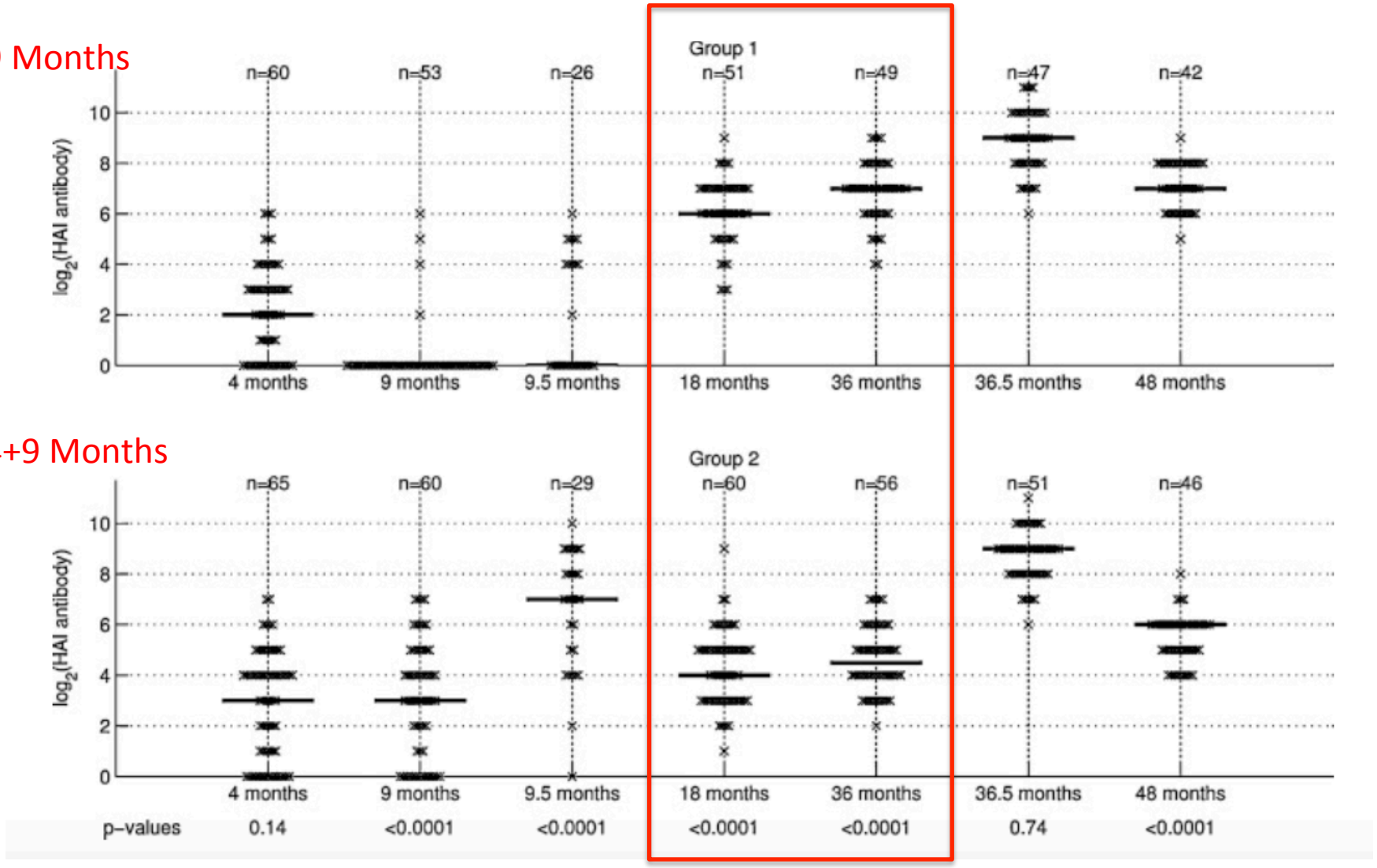
Age at time of vaccination, antibodies present	GMT (95% CI), mIU			SC, no./total (%)		SP, no./total (%)	
	Before vaccination	After first dose	After second dose	After first dose	After second dose	After first dose	After second dose
6 months							
Total	8 (4–16)	130 (58–292)	702 (344–1457)	25/29 (86)	25/29 (86)	15/29 (52)	25/29 (86)
PA	47 (31–71)	39 (16–95)	613 (174–1058)	11/15 (73)	13/15 (87)	4/15 (27)	12/15 (80)
NPA	NA	516 (209–1274)	1231 (511–3105)	14/14 (100)	12/14 (86)	11/14 (79)	13/14 (93)
9 months							
Total	2 (2–4)	835 (317–1882)	1546 (686–3484)	20/21 (95)	19/21 (90)	19/21 (90)	19/21 (90)
PA	27 (16–47)	70 (3–1890)	258 (27–2463)	3/4 (75)	4/4 (100)	2/4 (50)	3/4 (75)
NPA	NA	1496 (953–2350)	2356 (956–5811)	17/17 (100)	15/17 (88)	17/17 (100)	16/17 (94)
12 months, NPA	NA	1512 (1155–1984)	NA	78/80 (98)	NA	77/80 96)	NA

NOTE. The single (or first) dose of measles was administered as Attenuvax at age 6 and 9 months and as measles-mumps-rubella (MMR)–II at age 12 months. The second dose of measles was administered as MMR-II at age 12 months to infants who had been originally vaccinated at age 6 or 9 months. CI, confidence interval; GMT, geometric mean titer; NPA, no passive antibodies present at the time of the initial measles vaccination; PA passive antibodies present at the time of the initial measles vaccination; SC, seroconversion (defined as a 4-fold increase in antibody titer after the first dose of measles and an equivalent or greater antibody titer after the second measles dose); SP, seroprotection (defined as GMT >120 mIU).

Presence or absence of passive antibody most important determinant of antibody levels

Gans HA, Yasukawa LL, Alderson A, Rinki M, DeHovitz R, Beeler J, Audet S, Maldonado Y, Arvin AM. Humoral and cell-mediated immune responses to an early 2-dose measles vaccination regimen in the United States. J Infect Dis. 2004;190:83-90.

Early Two Dose (4+9) vs. 9 Months



Njie-Jobe J1, Nyamweya S, Miles DJ, van der Sande M, Zaman S, Touray E, Hossin S, Adetifa J, Palmero M, Burl S, Jeffries D, Rowland-Jones S, Flanagan K, Jaye A, Whittle H. Immunological impact of an additional early measles vaccine in Gambian children: responses to a boost at 3 years. Vaccine 2012;30:2543-50.

Early Two Dose (4.5+9) vs. 9 Months

Table 2. Proportion of Children With Nonprotective Antibody (Ab) Levels and Geometric Mean Titers (GMTs), by Age at Receipt of Edmonston-Zagreb Measles Vaccine and Number of Doses

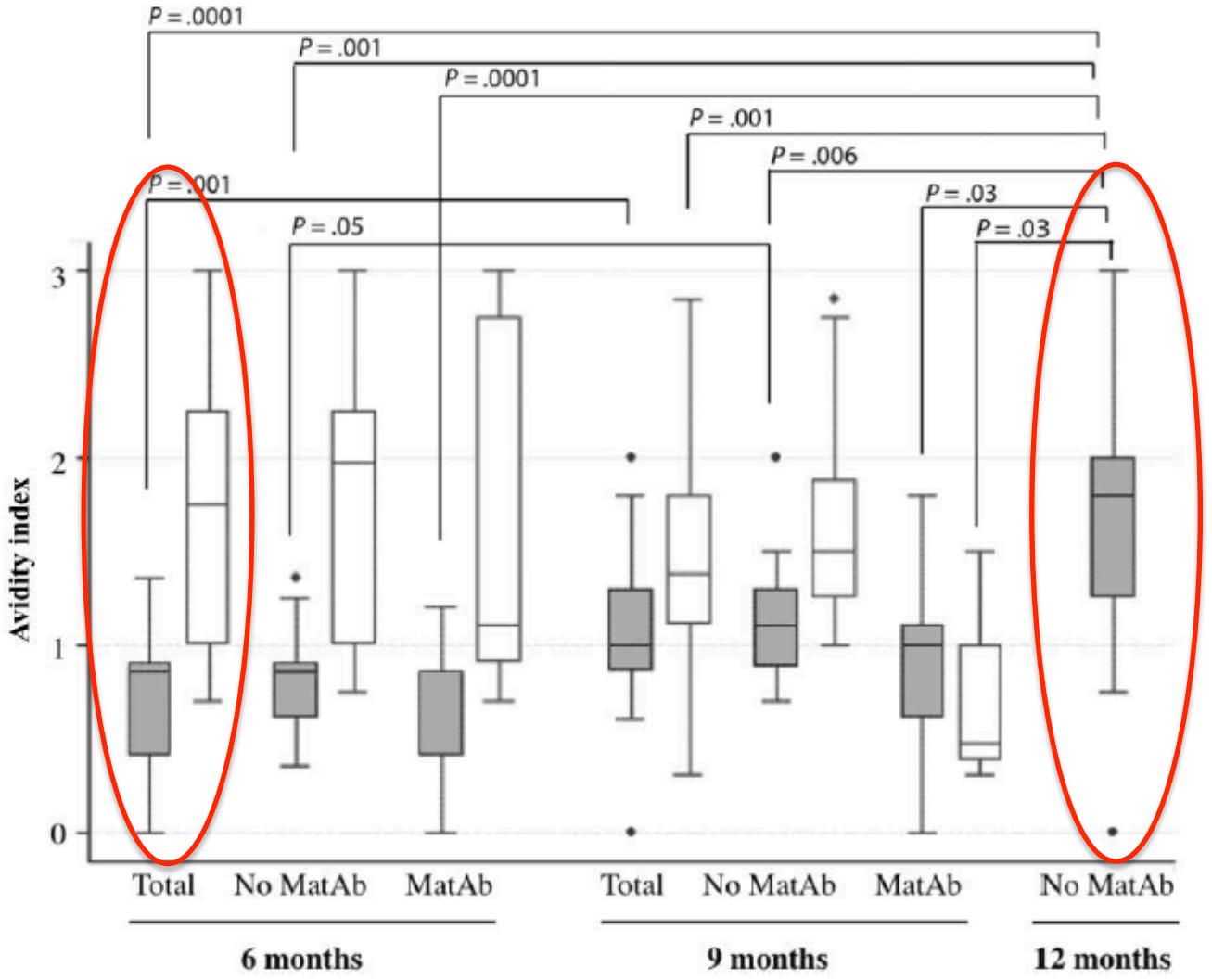
	Vaccination at 4.5 and 9 Mo (Group I)		Vaccination at 9 Mo or at 9 and 18 Mo (Group III)	
Age at Sampling	Nonprotective Ab Level, % (Proportion) [No. Nondetectable]	GMT, mIU/mL (95% CI)	Nonprotective Ab Level, % (Proportion) [No. Nondetectable]	GMT, mIU/mL (95% CI)
4.5 mo	75.2 (327/435) [199]	42 (38–48)	NA	NA
9 mo	22.6 (92/408) [35]	215 (188–243)	92.1 (382/415) [360]	23 (20–2479)
18 mo	NA	NA	0.9 (3/344) [1]	948 (927–977)
24 mo	3.3 (11/337) [2]	657 (581–744)	9 and 18 mo: 1.8 (3/167) [0]; only 9 mo: 0.7 (1/151) [0]	9 and 18 mo: 1246 (1058–1467); only 9 mo: 1287 (1067–1553)

Group I had significantly higher antibody levels at 9 months of age than group III ($P < .0001$). At 24 months of age, the GMT of group III was significantly higher than that for group I ($P < .0001$).

Abbreviations: CI, confidence interval; NA, not applicable.

Martins C, Garly ML, Bale C, Rodrigues A, Njie-Jobe J, Benn CS, Whittle H, Aaby P. Measles virus antibody responses in children randomly assigned to receive standard-titer edmonston-zagreb measles vaccine at 4.5 and 9 months of age, 9 months of age, or 9 and 18 months of age. J Infect Dis 2014;210:693-700.

Antibody Avidity



Nair N, Gans H, Lew-Yasukawa L, Long-Wagar AC, Arvin A, Griffin DE. Age-dependent differences in IgG isotype and avidity induced by measles vaccine received during the first year of life. J Infect Dis. 2007;196:1339-45.

Antibody Avidity

Table 1. Measles Immunity in Children Aged 5–10 Years After an Early Vaccine Regimen

Age at Time of Primary Measles Immunization[a]	No. of Measles Vaccine Doses	Interval Between Last Vaccine Dose and Blood Draw, Mean in Years (range)	GMC, mIU/mL (95% CI)[b]	Avidity Index, Mean[c]	Stimulation Index (±SE)[d]
6 mo (n = 26)	3	2.3 (1–5)	199 (110–361)	1.4	11.4 (1.3)
9 mo (n = 23)	3	2.8 (1–6)	419 (254–690)	1.7	10.9 (1.5)
12 mo (n = 21)	2	2.8 (1–6)	823 (544–1244)	2.2	14.4 (2.1)

Abbreviations: CI, confidence interval; GMC, geometric mean concentration; SE, standard error.

[a] First measles dose given as Attenuvax at 6 or 9 months of age or measles, mumps, and rubella virus vaccine live (MMRII) at 12 months of age; second dose given as MMRII at 12 months of age to infants given Attenuvax at 6 or 9 months of age or at 5 years of age to infants administered MMRII at 12 months of age; third dose given as MMRII at 5 years of age to children given Attenuvax at 6 or 9 months of age and MMRII at 12 months of age.

[b] Measured using plaque reduction neutralization test.

[c] Measured using enzyme immunoassay avidity assay.

[d] Measured using lymphoproliferation assay.

Gans HA, Yasukawa LL, Sung P, Sullivan B, DeHovitz R, Audet S, Beeler J, Arvin AM. Measles humoral and cell-mediated immunity in children aged 5-10 years after primary measles immunization administered at 6 or 9 months of age. J Infect Dis. 2013;207:574-82.

Vaccine Effectiveness

35% of children who received MCV1 <12 months developed measles compared to 2% who were revaccinated in a 1975 measles outbreak in Detroit

Shasby DM, Shope TC, Downs H, Herrmann KL, Polkowski J. Epidemic measles in a highly vaccinated population. N Engl J Med. 1977;296:585-9.

Vaccine Effectiveness

45 measles cases in Florida 1988 to 1996
"Early" two-dose schedule (6-11 + 12-18)
VE "early" two-dose = 99.5%
VE single 12-18 = 99.7%
VE single 6-11 = 97.6

Hutchins SS, Dezayas A, Le Blond K, Heath J, Bellini W, Audet S, Beeler J, Wattigney W, Markowitz L. Evaluation of an early two-dose measles vaccination schedule. Am J Epidemiol.2001;154:1064-71.

Vaccine Effectiveness

13,892 reported measles cases in Niamey, Niger
January 1, 1995, to May 7, 1995
Retrospective cohort study

First Author	Year	Country	MCV1	MCV2	Age at 1st dose	Age at 2nd dose	VE 1	VE 2
Kaninda	1998	Niger	SW	-	6	-	78	
			SW	SW	**6**	9		**93**
			SW	-	9	-	95	

Kaninda AV, Legros D, Jataou IM, Malfait P, Maisonneuve M, Paquet C, Moren A. Measles vaccine effectiveness in standard and early immunization strategies, Niger, 1995. Pediatr Infect Dis J. 1998;17:1034-9.

Conclusions

High prevalence of seropositivity following early two-dose schedule

No evidence of immunological tolerance

Evidence of lower antibody concentrations in children who received MCV1 younger than 9 months of age

Biological mechanism is likely presence of pre-existing neutralizing antibodies that impedes replication of vaccine virus

Assay variability and lack of strict correlate of protection hinder interpretation of significance of lower antibody concentrations

Some data on antibody avidity and cellular immunity following early two-dose schedule

Limited data suggest early two-dose schedule is effective

“Elephant in the Room”

Non-specific beneficial effects of early measles vaccination on child mortality

Aaby P, Martins CL, Ravn H, Rodrigues A, Whittle HC, Benn CS. Is early measles vaccination better than later measles vaccination? Trans R Soc Trop Med Hyg 2015;10:16-28.