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Reduced Antibody Response to Infant Measles Vaccination: Effects Based on Type and Timing of the First Vaccine Dose Persist After the Second Dose

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Background. The effect of age at first dose on the immunogenicity of a 2-dose pediatric schedule of measles-mumps-rubella (MMR) or measles-mumps-rubella-varicella (MMRV) vaccine was assessed in children born to mostly vaccinated mothers.

Methods. Immunogenicity data among children given their first measles vaccine dose between 11 and 22 months of age were pooled from 5 randomized controlled trials conducted in Europe and the United States between 2004 and 2010. Measles antibody titers were measured by enzyme-linked immunosorbent assay before and after each dose; geometric mean concentrations (GMCs) and the proportion seronegative (GMC <150 mIU/mL) were derived by age at first dose.

Results. Among 5542 children given a first measles vaccine dose at 11, 12, 13–14, and 15–22 months of age, the proportion seronegative decreased from 8.5% to 3.2%, 2.4%, and 1.5%, respectively ($P < .001$), whereas GMCs increased with older age measles vaccine initiation ($P < .001$). MMRV induced higher GMCs than MMR ($P < .001$). First and second dose GMCs were highly correlated (Spearman coefficient = 0.8).

Conclusions. As previously noted among infants born to mothers with history of wild-type measles, antibody responses among children born to vaccinated mothers were reduced based on earlier administration of their first measles vaccine dose at ≤12 vs ≥15 months of age. Negative effects of earlier age at first measles vaccine dose persisted after the second dose. The measles elimination goal may require a careful balance between earlier infant protection and the risk of reduced antibody responses and secondary vaccine failure among successive birth cohorts systematically initiated to measles vaccination <15 months of age.

Keywords. measles vaccine; immunogenicity; age; MMRV; vaccine failure.

All regions of the World Health Organization now have measles elimination targets [1]. To achieve elimination, high levels of immunity need to be maintained through high vaccine coverage and a minimum proportion of vaccine failures. With 1-dose programs, a greater risk of primary vaccine failure was observed in association with first vaccination at ≤12 months vs ≥15 months of age [2, 3]. These failures were believed to be due to maternal antibody interference on the active infant immune response to measles vaccination [4]. When countries opted for 2-dose programs, age at first dose was devalued because children who experienced primary vaccine failure generally seroconverted after the second dose [5, 6], and were considered protected. In addition, in countries such as Canada or the United States where measles vaccination programs have been in place for >40 years, primary vaccine failure was considered less likely because vaccinated mothers would transfer fewer measles antibodies [7]. However, vaccine failures have continued to represent 13%–44% of measles cases reported in several large outbreaks [8–11] and, in 2 epidemics, up to 14% of cases had received at least 2 measles vaccine doses [9, 10]. Epidemic investigations have shown increased risk of disease among 2-dose recipients when the first dose was administered at a younger age [12, 13].

We evaluated the effect of age at first dose on the immunogenicity of measles-containing vaccines (MCVs) among children born to mostly vaccinated mothers. We compared this effect among measles-mumps-rubella (MMR) and measles-mumps-rubella-varicella (MMRV) vaccine recipients and assessed the correlation between first- and second-dose antibody responses.

METHODS

Study Design

Post hoc meta-analysis of the combined data from 5 randomized controlled trials (RCTs) were originally conducted to evaluate the immunogenicity and safety of the tetravalent vaccine MMRV (RCTs MMRV-038, MMRV-043, MMRV-044)

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[14–17], the trivalent vaccine MMR (MMR-157), or the efficacy of MMRV against varicella (OKAH-179) [18]. Four multicenter RCTs were conducted in 13 European countries (Germany, Austria, Finland, Greece, Poland, Czech Republic, Italy, Lithuania, Norway, Romania, Russian Federation, Slovakia, and Sweden) between 2004 and 2008. RCT MMR-157 was conducted in the United States between 2010 and 2012. In all studies, children were followed for 12 weeks after their first vaccination and in RCTs MMRV-038, MMR-157, and OKAH-179, there was annual follow-up 2 or 3 years after vaccination.

Participants

Healthy 9- to 23-month-old children were recruited after written parental/guardian consent. Exclusion criteria precluded previous MMR or MMRV vaccination or known exposure to these diseases; vaccination with other products 30 days before or during the study; personal or family history of immunosuppressive condition; neurological disorder; or history of allergy related to the vaccination. For this analysis, children aged <11 months or >22 months and those seropositive for measles before vaccination were excluded.

Vaccination and Laboratory Analysis

Children were randomized to receive either 2 doses, separated by 6 weeks, of the MMRV vaccine Priorix-tetra; or coadministration of the MMR vaccine Priorix with varicella vaccine Varilrix, followed by a second dose of MMR vaccine Priorix, both MCVs containing the Schwarz strain. Children in RCT MMR-157 were randomized to receive only a single MMR dose as Priorix or M-M-RII. The latter includes the Moraten measles strain and was analyzed separately even if the genome of the 2 strains is identical [19].

Blood samples were collected before and 6 weeks after each vaccination. Measles antibodies were measured in sera with the Enzygnost (Behring) enzyme-linked immunosorbent assay (ELISA), with a cutoff value corresponding to 150 mIU/

Table 1. Inclusion and Characteristics of the Study Population

	Randomized Controlled Trial Number					
Characteristic	MMRV-038	MMRV-043	MMRV-044	MMR-157	OKAH-179	Total
Recruited	494	1438	970	1259	1880[a]	6041
Vaccination dose 1	494 (100)	1438 (100)	969 (99.9)	1220 (96.9)	1880 (100)	6001 (99.3)
Vaccination dose 2	470 (95.1)	1386 (96.4)	934 (96.3)	0 (0)	1778 (94.6)	4568 (75.6)
Exclusions	25 (5.1)	48 (3.3)	43 (4.4)	219 (17.4)	117 (6.2)	452 (7.5)
No vaccination	0 (0)	0 (0)	1 (0.1)	39 (3.1)	0 (0)	40 (0.7)
No prevaccination results	6 (1.2)	2 (0.1)	6 (0.6)	29 (2.3)	18 (1.0)	61 (1.0)
Positive prevaccination	8 (1.6)	25 (1.7)	16 (1.6)	6 (0.5)	17 (0.9)	72 (1.2)
No postvaccination results	8 (1.6)	20 (1.4)	10 (1.0)	145 (11.5)	82 (4.4)	265 (4.4)
Age <11 or >22 mo	3 (0.6)	1 (0.1)	10 (1.0)	0 (0)	0 (0)	14 (0.2)
Inclusions in the study	469 (94.9)	1390 (96.7)	927 (95.6)	1040 (82.6)	1763 (93.8)	5589 (92.5)
Age, mo						
11	3 (0.6)	147 (10.6)	254 (27.4)	0 (0)	5 (0.3)	409 (7.3)
12	101 (21.5)	251 (18.1)	260 (28.0)	810 (77.9)	414 (23.5)	1836 (32.9)
13–14	180 (38.4)	522 (37.5)	253 (27.3)	206 (19.8)	548 (31.1)	1709 (30.6)
15–22	185 (39.5)	470 (33.8)	160 (17.3)	24 (2.3)	796 (45.1)	1635 (29.2)
Male sex	242 (51.6)	723 (52.0)	486 (52.4)	536 (51.5)	913 (51.8)	2900 (51.9)
Country						
Germany	427 (91.0)	482 (34.7)	927 (100)	0 (0)	0 (0)	1836 (32.9)
Poland	0 (0)	456 (32.8)	0 (0)	0 (0)	194 (11.0)	650 (11.6)
United States	0 (0)	0 (0)	0 (0)	1040 (100)	0 (0)	1040 (18.6)
Other[b]	42 (9.0)	452 (32.5)	0 (0)	0 (0)	1569 (89.0)	2063 (36.9)
Inclusions dose 1 analysis	462 (93.5)	1376 (95.7)	917 (94.5)	1040 (82.6)	1747 (92.9)	5542 (91.7)
Inclusions dose 2 analysis	463 (93.7)	1358 (94.4)	904 (93.2)	0 (0)	961 (51.1)	3686 (61.0)
1-y follow-up	384 (77.7)	0 (0)	0 (0)	904 (71.8)	866 (46.1)	1250 (20.7)[c]
Inclusions year 1 analysis	377 (76.3)	0 (0)	0 (0)	0 (0)	851 (45.3)	1228 (20.3)
2-y follow-up	360 (72.9)	0 (0)	0 (0)	793 (63.0)	811 (43.1)	1171 (19.4)[c]
Inclusions year 2 analysis	343 (69.4)	0 (0)	0 (0)	0 (0)	779 (42.5)	1122 (18.6)
3-y follow-up	293 (59.3)	0 (0)	0 (0)	0 (0)	0 (0)	293 (4.9)
Inclusions year 3 analysis	267 (54.0)	0 (0)	0 (0)	0 (0)	0 (0)	267 (4.4)

Data are presented as No. (column %).

Abbreviations: MMR, measles-mumps-rubella; MMRV, measles-mumps-rubella-varicella; OKAH, efficacy of MMRV against varicella.

[a]Children recruited for the serological component of the study.

[b]Austria, Czech Republic, Finland, Greece, Italy, Lithuania, Norway, Romania, Russian Federation, Slovakia, Sweden.

[c]Participants who received 2 doses of measles-containing vaccine (study MMRV-038 and OKAH-179).

mL. Antibody concentrations were expressed as geometric mean concentrations (GMCs), derived as antilog of the mean $\log_{10}$-transformed concentrations. Sera with undetectable antimeasles titers were assigned the arbitrary value of 75 mIU/mL for GMC derivation. Seroconversion was defined as a positive antibody titer among those with a negative prevaccination titer. Concentrations 150–499 mIU/mL arbitrarily defined a "low response" corresponding to approximately 2.5% of children post–dose 1.

Statistical Analysis

Individual subjects from the 5 databases were combined. GMCs 6 weeks after each measles dose and proportion showing seroconversion, stratified by type of MCV, were calculated for each age group. Age in months was modeled using indicator variables.

GMC ratios and relative risks (RRs) for seronegativity and low response were computed using 12 months as the reference age. Estimates were adjusted for the type of vaccine, the country, and the original study using, respectively, linear models of the $\log_{10}$ concentrations, and log binomial regression models (fitted using Poisson regression with robust standard errors when maximization of the binomial likelihood failed). All included the Dunnett adjustment for multiple comparisons. No change in the standard error was observed when using an estimator robust to heteroscedasticity; accordingly, results are presented with the usual mean squares estimator. Antibody response trends were also analyzed with age as a continuous variable. The Spearman correlation coefficient compared antibody response after the first and second dose.

For studies providing longer-term follow-up, we compared antibody response by age group 6 weeks and 1, 2, and 3 years post–second dose using generalized estimating equations for longitudinal data with an autoregressive working correlation matrix. To avoid the impact of missing observations due to attrition, the observed values were weighted by the inverse probability of censoring [20]. Because the GMC and seronegative ratios were not modified by time, a global measure is presented.

RESULTS

Study Population

Among the 6041 children recruited across the 5 RCTs with serologic testing, 5542 (92%) were analyzed for post–dose 1 results and 3686 (61%) for post–dose 2 results. Reasons for exclusion were no vaccination (n = 40); seropositivity prevaccination (n = 72); missing serologic results (n = 326); and age <11 months (n = 11) or >22 months (n = 3) at first dose. The longitudinal analysis included 1228 (20%), 1122 (19%), and 267 (4%) children vaccinated with 2 doses and followed during 1, 2, and 3 years, respectively. Participants without results post–dose 2 (n = 16), with missing values through the follow-up (n = 41), or aged 11 months (n = 6) were excluded. Among participants, 52% were males, 79% were white, and 33% were recruited in Germany, 19% in the United States, 12% in Poland, and <6% in each of the other countries (Table 1).

Immunogenicity

Six weeks after the first dose of MCV, 97.2% had seroconverted (96.8% with MMRV, 97.4% with MMR [Schwarz strain] and 99.6% with MMR [Moraten strain]; $P = .02$) (data not shown). The overall GMC was 2960 mIU/mL (3408, 2474, and 2942 mIU/mL, respectively; $P < .001$). The proportion seronegative following vaccination decreased significantly with older age at the first dose, from 8.5% in children vaccinated at 11 months to 3.2%, 2.4%, and 1.5% with vaccination at 12, 13–14, and 15–22 months, respectively ($P < .001$). This significant trend was seen both with MMRV ($P < .001$) and MMR (Schwarz strain) ($P < .001$) (Table 2). The trend was also observed but nonsignificant with MMR (Moraten strain), given the limited statistical power with 77% of children being vaccinated at 12 months. Similarly, the proportion of children with low response (150–499 mIU/mL) was greater with first dose at 11 months (7.5%) vs older ages (2.8%, 1.7%, 1.5% at 12, 13–14 and 15–22 months of age respectively), globally ($P < .001$) and for each vaccine ($P < .001$ and $P = .005$) (Figure 1). The GMC also steadily increased with older age at first vaccination, from 1835 mIU/mL (11 months) to 3562 mIU/mL (15–22 months) ($P < .001$; Table 2).

GMCs post–dose 2 were highly correlated with GMCs post–dose 1 (Spearman coefficient = 0.8) (Supplementary Figure 1). The pattern of improved antibody response with older age at first dose and MMRV vaccine persisted after the second dose (Table 2). Among the 119 children seronegative after their first dose and with information after the second dose, 23% still had an undetectable titer after a second dose, and this was observed more frequently with MMR (10/28 [36%]) than with MMRV (17/91 [19%]) ($P = .06$). Eight children seronegative post–dose 2 had detectable titers after the first dose. Sensitivity analysis excluding them did not change the results. While none of the 134 children with a concentration between 150 and 499 mIU/mL post–dose 1 were seronegative post–dose 2, their titers remained significantly lower than those with a higher first-dose response (610 [95% confidence interval {CI}, 538–691] mIU/mL vs 5138 [95% CI, 5016–5259] mIU/mL).

In multivariable analysis adjusting for the type of vaccine, the country, and the study, GMCs increased significantly with older age at first dose (Figure 2). Children vaccinated at 11 months had a 23% lower GMC and 30% increased risk of seronegativity compared with children vaccinated at 12 months of age. In children vaccinated with 1 dose at 13–14 or 15–22 months the GMCs were, respectively, 1.21 (95% CI, 1.1–1.3) and 1.37 (95% CI, 1.2–1.5) times greater than in children vaccinated at 12 months, and their adjusted RRs for seronegativity were 49% (RR, 0.51 [95% CI, .3–.8]) and 71% (RR, 0.29 [95% CI, .2–.5]) lower, respectively. After 2 doses, the association between the

Table 2. Antibody Titer Following the First and Second Doses of Measles-Containing Vaccines by Age at First Dose and Type of Vaccine

	Age at First Dose, mo					
	11	12	13–14	15–22	Total	*P* Value[a]
Post–first dose						
No.	402	1825	1696	1619	5542	
Seronegative	8.5% (34/402)	3.2% (58/1825)	2.4% (40/1696)	1.5% (25/1619)	2.8% (157/5542)	<.001
MMRV[b]	8.4% (27/320)	4.5% (29/644)	2.4% (24/1014)	1.5% (15/982)	3.2% (95/2960)	<.001
MMR (Schwarz)	8.5% (7/82)	2.9% (28/980)	2.5% (16/631)	1.6% (10/629)	2.6% (61/2322)	.0028
MMR (Moraten)	…	0.5% (1/201)	0.0% (0/51)	0.0% (0/8)	0.4% (1/260)	1.0000
1500001/mIU/mL	7.5% (30/402)	2.8% (51/1825)	1.7% (29/1696)	1.5% (24/1619)	2.4% (134/5542)	<.001
MMRV[b]	6.9% (22/320)	3.1% (20/644)	0.9% (9/1014)	0.7% (7/982)	2.0% (58/2960)	<.001
MMR (Schwarz)	9.8% (8/82)	2.8% (27/980)	3.2% (20/631)	2.7% (17/629)	3.1% (72/2322)	.0050
MMR (Moraten)	…	2.0% (4/201)	0.0% (0/51)	0.0% (0/8)	1.5% (4/260)	.6345
GMC, mIU/mL (95% CI)	1835 (16725(4/2)	2630 (25175(4/2)	3155 (3016–3301)	3562 (3401–(4/2)	2960 (2885–(4/2)	<.001
MMRV[b]	2051 (18481(4/2)	2887 (26821(4/2)	3632 (34251(4/2)	4199 (39561(4/2)	3408 (32931(4/2)	<.001
MMR (Schwarz)	1188 (9708(Sch)	2425 (2287(Schw)	2526 (2348(Schw)	2751 (2557(Schw)	2474 (2381(Schw)	<.001
MMR (Moraten)	…	2891 (2616ten)a)	3005 (2465ten)a)	3976 (2411ten)a)	2942 (2695ten)a)	.4572
Post–second dose						
No.	396	811	1248	1231	3686	
Seronegative	2.3% (9/396)	1.2% (10/811)	0.8% (10/1248)	0.5% (6/1231)	0.9% (35/3686)[c]	.0109
MMRV[b]	2.2% (7/317)	0.8% (5/638)	0.6% (6/995)	0.5% (5/966)	0.8% (23/2916)	.0232
MMR[b]	2.5% (2/79)	2.9% (5/173)	1.6% (4/253)	0.4% (1/265)	1.6% (12/770)	.1109
15009(12mIU/mL	7.1% (28/396)	2.8% (23/811)	1.0% (12/1248)	0.5% (6/1231)	1.9% (69/3686)	<.001
MMRV[b]	5.7% (18/317)	2.7% (17/638)	0.5% (5/995)	0.3% (3/966)	1.5% (43/2916)	<.001
MMR[b]	12.7% (10/79)	3.5% (6/173)	2.8% (7/253)	1.1% (3/265)	3.4% (26/770)	<.001
GMC, mIU/mL (95% CI)	2933 (26901(26/)	3983 (37491(26/)	4738 (45121(26/)	5442 (51811(26/)	4536 (44071(26/)	<.001
MMRV[b]	3392 (31011(26/)	4444 (41711(26/)	5360 (50951(26/)	6058 (57541(26/)	5098 (49391(26/)	<.001
MMR[b]	1635 (13221(26/)	2659 (23031(26/)	2917 (25891(26/)	3679 (32751(26/)	2916 (27421(26/)	<.001

Data are presented as % (no./No.) unless otherwise indicated.

Abbreviations: CI, confidence interval; GMC, geometric mean concentration; MMR, measles-mumps-rubella vaccine; MMWR, measles-mumps-rubella-varicella vaccine.

[a] χ^2 or exact Fisher test for seronegativity and low response; F-test for GMC.

[b] MMRV and MMR vaccines containing Schwarz strain unless otherwise indicated.

[c] Eight of the 35 seronegative post–dose 2 patients seroconverted after dose 1.

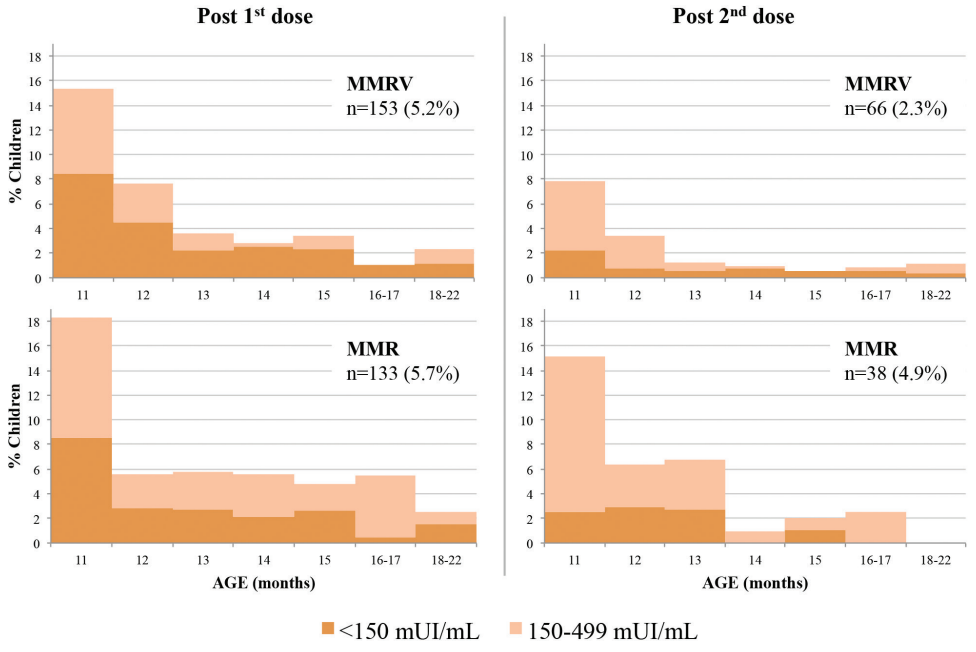

Figure 1. Age distribution of children with low and negative response after vaccination with 1 or 2 doses of measles-containing vaccine. Includes children who received measles-mumps-rubella-varicella (MMRV) vaccine and measles-mumps-rubella (MMR) vaccine containing Schwarz strain.

age at first dose and the GMC was slightly weaker but still significant (GMC ratios of 0.82, 1.15, and 1.32 for 11, 13–14, and 15–22 months vs 12 months). Compared to children first vaccinated at 12 months, the adjusted proportion seronegative was 30% higher for those vaccinated at 11 months but 28% and 52% lower for those vaccinated at 13–14 and 15–22 months, respectively. However, the latter comparisons did not reach statistical significance (Table 3).

When analyzed as a continuous variable, age at first dose showed a significant log-linear relationship with GMCs after 1 dose ($P < .001$) and 2 doses ($P < .001$) and with the prevalence of seronegativity after the first dose ($P < .001$) and second dose ($P = .03$) (Table 3).

Antibody Geometric Mean Concentrations 1–3 Years Post–Dose 2

In 2-dose recipients, the adjusted GMC decreased with time, at 3 years diminishing to levels similar to those measured 6 weeks after the first dose (Figure 3). Thus, the initial increase of antibody levels 6 weeks after the second vaccination was not maintained in any age group 3 years later. In repeated measures analysis over the 3 years postvaccination, the GMC was 40% higher in children first vaccinated at 15–22 months compared with 12 months (GMC ratio, 1.4 [95% CI, 1.2–1.6]), and the adjusted seronegative RRs were 0.9 (95% CI, .2–3.7) for a first dose at 13–14 months and 0.3 (95% CI, .1–1.3) for 15–22 months, both compared to 12 months (Table 4).

DISCUSSION

In this study, immunogenicity of the measles vaccine improved significantly with first vaccination at 13–14 and ≥15 months compared to 12 months of age and was conversely significantly lower when administered at 11 months. The immunogenicity of MMRV was consistently higher than that of MMR but followed the same age-related pattern. When the response to the first dose was poor, the response to the second dose was also poor. Antibody concentrations declined shortly after the second dose with a return toward the concentration obtained after first immunization.

When programs included only a single dose of measles vaccine, vaccinated cases were considered to be mostly due to primary vaccine failure and rarely to waning immunity [21]. In 2-dose programs, the second dose was intended to seroconvert children who did not respond to the first dose, not to boost antibody levels. As most children who failed to seroconvert after a first dose seroconverted after a second dose [4], the lower protection associated with a first dose administered at 12 (vs 15) months of age was expected to be overcome by 2-dose programs. However, in Finland, a higher risk (RR, 3.5) of measles was reported in twice-vaccinated children whose first dose was administered before rather than after 14 months [12]. Similarly, the 2011 outbreak in Canada identified a 3-fold greater risk of measles when the first dose was administered at 12 rather than ≥15 months of age in 2-dose recipients [13].

As these findings were observed mostly in individuals born to mothers who had had wild measles, it was unclear if it could be extrapolated to children born instead to vaccinated mothers. In the current study, the information about vaccination or disease in the mothers of participants was not available. However, given that measles vaccination programs were introduced in the United States in the 1960s and in Europe in the 1970s [22], the vast majority of children born after 2003 were likely born to vaccinated women. In these children, maternal antibody interference was not expected to pose a problem by 12 months of

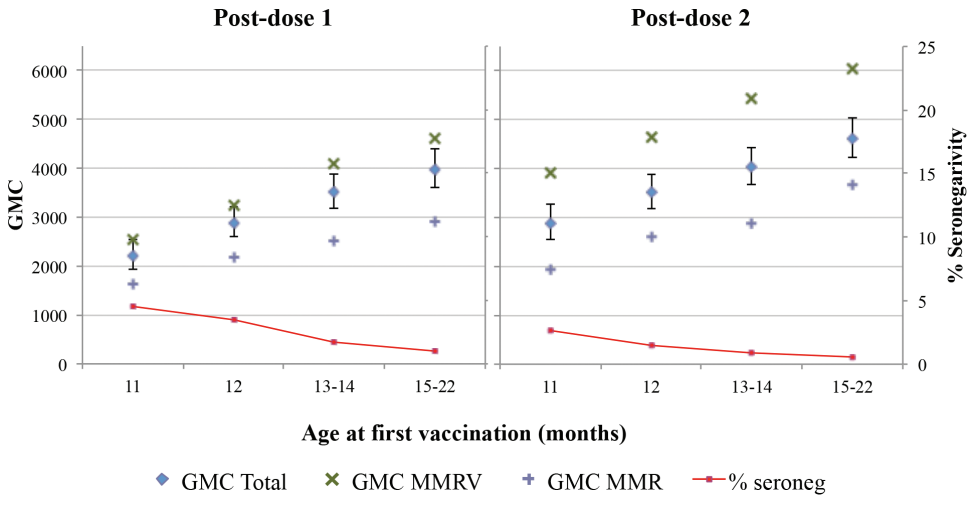

Figure 2. Geometric mean concentrations (GMCs) and proportion seronegative after 1 and 2 doses of measles-containing vaccine by age at first vaccination. Included the children receiving measles-mumps-rubella-varicella (MMRV) vaccine and measles-mumps-rubella (MMR) vaccine containing Schwarz strain. Post–dose 1: Total GMCs and proportion seronegative adjusted for type of vaccine, country, and study; GMCs for MMRV and MMR adjusted for country and study. Post–dose 2: Total GMCs adjusted for type of vaccine, country, and study; proportion seronegative adjusted for type of vaccine; GMCs for MMRV and MMR adjusted for country and study.

Table 3. Geometric Mean Concentration Ratios and Seronegativity Risk Ratios After 1 and 2 Doses of Measles-Containing Vaccine by Age at First Vaccination

Age at First Dose, mo	Post–First Dose (n = 5542)				Post–Second Dose (n = 3686)			
	GMC Ratio (95% CI) Crude	Adjusted[a]	SRR (95% CI) Crude	Adjusted[b]	GMC Ratio (95% CI) Crude	Adjusted[a]	SRR (95% CI) Crude	Adjusted[c]
11	0.70 (.61–.80)	0.77 (.66–.88)	2.66 (1.62–4.36)	1.30 (.76–2.23)	0.74 (.65–.84)	0.82 (.73–.93)	1.84 (.62–5.44)	1.30 (.43–3.95)
12[d]	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
13–14	1.20 (1.10–1.30)	1.21 (1.10–1.32)	0.74 (.46–1.20)	0.51 (.31–.84)	1.19 (1.08–1.31)	1.15 (1.05–1.26)	0.65 (.23–1.86)	0.73 (.25–2.10)
15–22	1.35 (1.25–1.47)	1.37 (1.25–1.51)	0.49 (.28–.85)	0.29 (.16–.54)	1.37 (1.24–1.50)	1.32 (1.20–1.45)	0.40 (.12–1.34)	0.48 (.14–1.66)
P value[e]	<.001	<.001	<.001	<.001	<.001	<.001	.0229	.2889
Per month[f]	1.07 (1.06–1.08)	1.06 (1.05–1.08)	0.59 (.45–.78)	0.56 (.43–.72)	1.07 (1.06–1.08)	1.06 (1.04–1.07)	0.51 (.32–.82)	0.63 (.40–.99)
P value[f]	<.001	<.001	<.001	<.001	<.001	<.001	.0015	.0272

Abbreviations: CI, confidence interval; GMC, geometric mean concentration; SRR, seronegativity risk ratio.

[a]Linear model adjusted for type of vaccine, country, and study, with Dunnett adjustment for multiple comparisons.

[b]Log-binomial regression model adjusted for type of vaccine, country, and study, with Dunnett adjustment for multiple comparisons.

[c]Log-binomial regression model adjusted for type of vaccine and study, with Dunnett adjustment for multiple comparisons.

[d]Reference age group.

[e]Wald test for age.

[f] Estimations with age as a continuous variable. Wald test for log-linear trend with age in the GMC and the seronegativity risk.

age. Indeed, the proportion who remained seronegative (primary vaccine failures) following 2 doses of MCV was very small whatever the age at first dose or the type of vaccine used. However, the proportion of children seronegative or with low concentrations (150–499 mIU/mL) was greater in those first vaccinated at 12 compared with ≥15 months of age.

With antibody decline over time, it is likely that children with low concentrations immediately after the second dose become at risk for secondary vaccine failure. Loss of protective antibody concentrations 6 years after revaccination has also been demonstrated in 36% of 33 students with initial low levels of antibodies post–dose 1 [23]. Although the proportion who will eventually become susceptible to measles is unknown, it is interesting to note that the proportions of children with concentrations <500 mIU/mL after 2 doses, if first vaccinated at age 12 months (6.5%) or ≥15 months (1.5%), are similar to the proportions of vulnerable adolescents despite 2 doses of MMR observed during the 2011 Canadian outbreak: 7% (93% vaccine effectiveness) and 2.5% (97.5% vaccine effectiveness), respectively [13]. Our results are also consistent with those from a

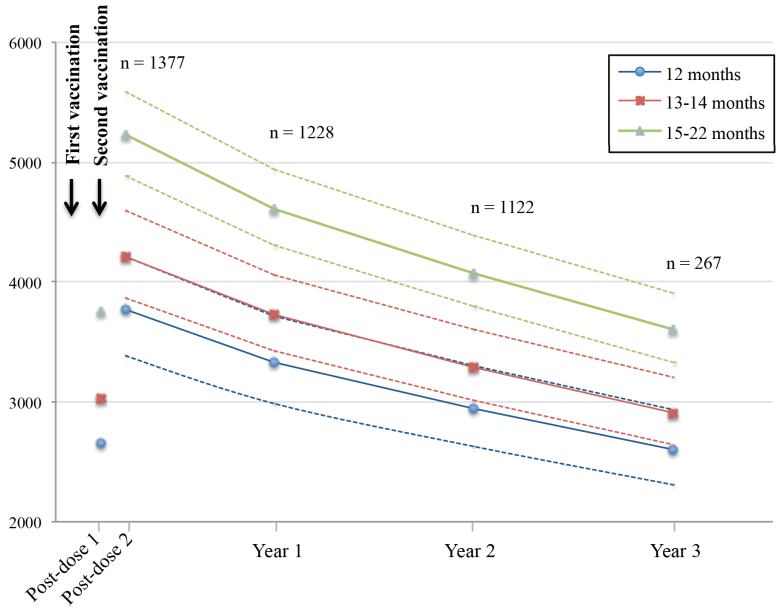

Figure 3. Three-year follow-up of geometric mean concentrations (GMCs) by age at first vaccination. GMCs calculated using generalized estimating equations for correlated data, adjusted for type of vaccine and country, and weighted using the inverse probability of censoring. Titers post–first dose are presented for comparability. Dotted lines represent 95% confidence intervals.

Table 4. Antibody Titer Post–Second Dose Among Children With 1, 2, or 3 Years of Follow-up by Age at First Vaccination

	Age at First Vaccination, mo			
	12	13–14	15–22	Total
Post–dose 2, No.	297	481	599	1377
Seronegative	0.5% (.2–1.3)	0.5% (.1–1.6)	0.1% (.0–.5)	
150–499 mIU/mL	2.6% (1.4–5.0)	1.6% (1.0–2.5)	0.6% (.3–1.2)	
GMC	3771 (3381–4205)	4216 (3872–4591)	5223 (4879–5590)	
Year 1, No.	253	426	549	1228
Seronegative	0.8% (.4–2.0)	0.8% (.3–1.9)	0.2% (.1–.7)	
150–499 mIU/mL	2.8% (1.5–5.1)	1.6% (1.1–2.6)	0.6% (.3–1.2)	
GMC	3333 (2985–3721)	3726 (3420–4060)	4615 (4312–4941)	
Year 2, No.	225	389	508	1122
Seronegative	1.3% (.5–3.7)	1.2% (.6–2.6)	0.4% (.1–1.0)	
150–499 mIU/mL	3.0% (1.6–5.4)	1.8% (1.1–2.8)	0.7% (.3–1.3)	
GMC	2946 (2628–3302)	3293 (3011–3601)	4079 (3796–4384)	
Year 3, No.	58	107	102	267
Seronegative	2.2% (.6–7.9)	2.0% (.9–4.5)	0.6% (.2–1.8)	
150–499 mIU/mL	3.2% (1.7–6.0)	1.9% (1.1–3.2)	0.7% (.4–1.4)	
GMC	2603 (2308–2936)	2910 (2644–3203)	3605 (3330–3903)	
SRR	1.0	0.9 (.2–3.7)	0.3 (.1–1.3)	
GMC ratio	1.0	1.1 (1.0–1.3)	1.4 (1.2–1.6)	

Data in parentheses indicate 95% confidence intervals.

GMCs are adjusted for type of vaccine and the country; proportion of seronegativity and proportion of low response (150–499 mIU/mL) are adjusted for type of vaccine; all are weighted using the inverse probability of censoring.

Abbreviations: GMC, geometric mean concentration; SRR, seronegativity risk ratio.

large serological survey where seronegativity in twice-vaccinated German children declined with an age at first dose, moving from <12 up to 17 months and increasing with a longer interval since the last dose [24].

While some participants who were seronegative at the screening test may have had maternal antibodies given the threshold of detection for the ELISA, poorer immunogenicity at 11 vs 12 months may also be explained by immaturity of the immune system. Indeed, in children with no maternal antibodies detectable by the sensitive plaque reduction neutralization assay (PRN), both the humoral and cellular immune response improved with older age at first dose (from 6 to 9 to 12 months) and 4% of those receiving MMR at 12 months remained seronegative, a proportion similar to what we observed [25]. If immaturity of the immune system may explain the response associated with age at first dose in children born to vaccinated mothers [26, 27], the high correlation between antibody concentrations after the first and second dose and the return to pre–second dose levels with time are concerning signals that have also been reported elsewhere [23, 28, 29]. As a poor response to an early first dose is not overcome in a durable manner by a second dose, it is unclear whether the effect of earlier age at first vaccine dose may be remediable with additional doses, or for how long. This is critical to understand in the context of the measles elimination goal and successive cohorts of children systematically vaccinated with measles vaccine for the first time at <15 months of age.

The strength of this study is its large number of RCT participants from several countries who underwent similar protocols and were tested with the same standardized ELISA test, optimizing the validity and generalizability of the results and providing good sample size for a precise analysis of the modifying effect of age at first dose. Nevertheless, this study has limitations. The original trials were randomized to compare 2 vaccines and not vaccination schedules. We cannot rule out some residual confounding from factors such as differential exposure to wild virus or maternal status between different age groups, but this seems most unlikely considering the similar low prevalence of seropositivity before vaccination (0.5% in the United States and 1.4% in Europe who were excluded). With a sensitivity of 88% to detect low PRN titers, the Enzygnost ELISA [30] may have missed some children with low levels of measles neutralizing antibodies potentially interfering with the vaccine [23, 31], but with a nearly 100% sensitivity to detect protective PRN titers of ≥120 [30], our conclusions about individual and population vulnerability after vaccination seem robust. The interval between doses was short (6 weeks) but considering the high seropositivity rate, it is unlikely that a longer interval would have changed our conclusions. The greatest limitation is the clinical relevance of immunogenicity data [32]. The interpretation that low antibody levels shortly after a second dose may not be protective over the long term is speculative; protective cellular immunity may exist in the absence of antibody response [33]. However, a correlation between low antibody titers and measles susceptibility has been shown in prior epidemic analysis [34] and our results align well with data from outbreak investigations [12, 13].

Measles elimination requires the maintenance of population immunity above 92%–94% [1]. In pursuit of that goal, strategies need not only to maintain the highest vaccine coverage but also to minimize the proportion of both primary and secondary vaccine failures. In elimination settings, whereas the epidemiology is mostly driven by lack of vaccination, some vaccinated individuals acquire measles that may be mild [34, 35] but contributes to transmission [36, 37]. In this context, the additional protection of 3%–5% of vaccinated children against secondary vaccine failures by postponing the first dose from 12 to 15 months of age would be significant and the risk would be minimal in countries that achieved elimination. As an example, measles incidence was 0.7 per 100 000 in infants aged 6–11 months in the United States between 2009 and 2014, and 1.3 per 100 000 in infants aged <1 year in Canada between 2002 and 2013 [38, 39]. Many of these infant cases were from families with philosophical or religious objections. This suggests that within families that accept vaccination, the measles risk for infants whose vaccination is delayed to 15 months of age would be much lower than 1 per 100 000. The much greater proportion of children seronegative or with low titers when their first dose is administered at 11 rather than 12 months of age may be a greater concern in the context of policies that recommend vaccination as early as 9 months for infant daycare entry.

Ultimately, these and other findings suggest that the measles elimination goal may require a careful balance between earlier infant protection and the risk of secondary vaccine failure among successive birth cohorts systematically initiated to measles vaccine <15 months of age.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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