

Long-term Neutralizing Antibody Levels Against Measles and Rubella Viruses Among Adults With 3 Doses of Measles-Mumps-Rubella Vaccine

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Background. A third dose of measles-mumps-rubella vaccine (MMR) may be administered for various reasons, but data on long-term immunity are limited. We assessed neutralizing antibody levels against measles and rubella among adults up to 11 years after receipt of a third MMR dose.

Methods. In this longitudinal study, healthy adults who received a third MMR dose as young adults (ages 18–28 years) were recalled around 5 years and 9–11 years after the third dose. Measles and rubella antibody levels were assessed by plaque-reduction and immunocolorimetric neutralization assays, respectively. Antibody concentrations <120 mIU/mL and <10 U/mL were considered potentially susceptible to measles and rubella, respectively. Geometric mean concentrations (GMCs) and 95% confidence intervals (CIs) over time were estimated from generalized estimating equation models.

Results. Approximately 5 and 9–11 years after receipt of the third dose, 405 and 304 adults were assessed, respectively. Measles GMC was 428 mIU/mL (95% CI, 392–468 mIU/mL) 5 years postvaccination, declining to 381 mIU/mL (95% CI, 339–428 mIU/mL) 11 years postvaccination. At the last follow-up visit (9–11 years postvaccination), 10% of participants were potentially susceptible to measles infection. Rubella GMCs were stable throughout the follow-up period (63 U/mL to 65 U/mL); none of the participants was susceptible to rubella at the last follow-up visit.

Conclusions. Eleven years after receiving a third MMR dose, measles and rubella neutralizing antibody levels remained high in adults. However, on the basis of waning antibody levels, some adults may become susceptible to measles infection over time despite receipt of 3 vaccine doses.

Keywords. immunity; measles; MMR vaccine; rubella; third dose.

Measles and rubella are highly contagious viral infections that can cause serious illness, lifelong complications, and death. Two doses of measles-mumps-rubella (MMR)-containing vaccines are routinely recommended in childhood for prevention of measles, mumps, and rubella [1], and high 2-dose coverage contributed to the elimination of both measles and rubella in the United States (US). However, both diseases continue to occur worldwide [2, 3], and repeated measles importations into the US have led to recent outbreaks in communities with low

MMR vaccination coverage [4]. In 2019, more than 1200 measles cases were reported from 31 states, with outbreaks in undervaccinated, close-knit communities accounting for 85% of all cases [4]. Additionally, 42% of the 67 reported rubella cases from 2005 to 2011 were known importations, and all rubella patients reported since 2012 were infected outside the US [1, 5].

Since 2018, a third dose of MMR has been recommended to improve protection during mumps outbreaks among highly vaccinated populations [6]. Third doses of MMR are also administered in nonoutbreak settings to healthcare personnel, military recruits, international travelers, college students, and others who may have previously received 2 doses but lacked documentation of receipt. Women of childbearing age may also receive a third dose if they have rubella immunoglobulin G (IgG) antibody concentrations that are <10 IU/mL, the cut-off for rubella immunity, regardless of having 2 documented doses of MMR [1].

Given that adults can receive a third dose of MMR, especially during measles or mumps outbreaks, it is important to better understand the long-term immunity of a third MMR dose in the adult population. Several longitudinal studies have shown

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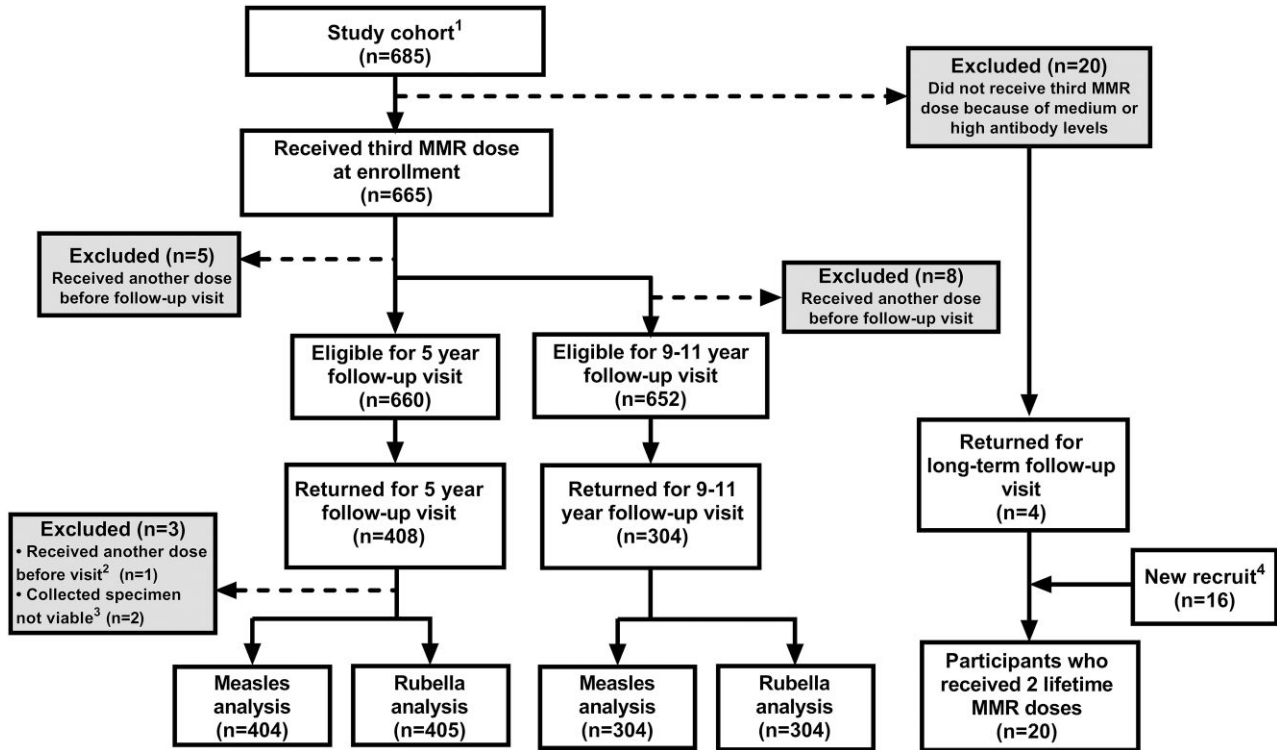


Figure 1. Flowchart of participants who were eligible for follow-up after receiving their third measles-mumps-rubella vaccine (MMR) dose in 2009–2010 and reenrolled at approximately 5 years and 9–11 years after receipt of a third MMR dose, as well as participants who were reenrolled after having had received only 2 MMR doses, approximately 24 years prior. ¹Participants of a longitudinal study assessing safety and short-term immunogenicity of a third MMR dose. ²Identified after completion of follow-up visit. ³Due to issues with shipping delays. ⁴Recruited from participants previously enrolled in a 12-year longitudinal study conducted in 1994–2007.

that measles and rubella virus antibodies wane with time since receipt of the second MMR dose [7–13]. Waning after receipt of the third dose is unknown, as immunity data on measles and rubella following a third dose have been limited to 3 years [14, 15]. In 2009, we initiated a study to assess safety and immunity of the third dose of MMR administered to young adults. Young adults were targeted because most cases during the resurgence of mumps in the US in mid-2000 occurred among 2-dose-vaccinated young adults [16] and because of concerns regarding the projected increase in the proportion of persons potentially susceptible to measles with increasing time since the second MMR dose [7]. In this report, we describe long-term neutralizing antibody levels against measles and rubella viruses among adults through 11 years after receipt of a third MMR dose.

METHODS

Study Design and Population

The initial cohort included 665 young healthy adults aged 18–28 years who received the third MMR dose in 2009–2010 and were followed for approximately 1 year to assess safety and short-term immunity [17–20]. Approximately 5 and 9–11 years after receipt of the third MMR dose, participants were invited to return for a

blood draw to assess long-term immunity. Any participants who received an additional MMR dose (ie, >3 total MMR doses) during follow-up were no longer eligible for subsequent study visits (Figure 1). The first long-term follow-up visit at 5 years after receipt of the third MMR dose occurred during 2014–2016. The second long-term follow-up visit, which occurred during 2019–2021 (9–11 years after the third MMR dose) was extended because of the coronavirus disease 2019 pandemic when in-person activities for research at the Marshfield Clinic Research Institute were restricted. At each visit, participants were asked about potential exposure to and illness from measles, mumps, and rubella; occupation; household composition; and history of foreign travel. In addition, during the follow-up visit in 2019–2021, we reenrolled participants who had not received 3 MMR doses from a previous longitudinal study that examined immunity following receipt of the second MMR dose [7, 12, 21]. These persons were included for the exploratory objective of comparing antibody levels among similar-age adults who received 3 versus 2 doses.

Laboratory Methods

Sera were collected, processed, and stored frozen at Marshfield Clinic Research Institute per standard procedures until shipped

to the Centers for Disease Control and Prevention (CDC) for serologic testing. For all assays, 10% of specimens were retested to confirm reproducibility.

Measles Virus Neutralizing Antibody

Measles virus neutralizing antibody concentrations were measured by plaque-reduction neutralization assay as previously described [22]. The World Health Organization second international standard anti-measles serum (IS, coded 66/202, supplied by the National Institute for Biological Standards and Control, South Mimms, United Kingdom) was used to calculate the reciprocal of the 50% endpoint titer by the Kärber method. The plaque-reduction neutralization assay and the standard used for the long-term evaluation were the same as those used for the short-term evaluation (up to 1 year after the third MMR dose) [17]; however, testing was conducted at CDC instead of the US Food and Drug Administration. Measles virus neutralizing antibody titers were expressed as a concentration (mIU/mL) with a titer of 1:8 corresponding to 8 mIU/mL. Participants with measles virus neutralizing antibody concentrations <120 mIU/mL were considered potentially susceptible to measles infection and those with concentrations \geq 120 mIU/mL were considered protected against measles infection [22–24].

Measles Virus-Specific Antibody Avidity

IgG avidity levels measure the binding strength between IgG antibodies and the virus and is an important characteristic of a mature antibody response [24]. Measles virus-specific IgG avidity was measured for participants with serum collected at 5 years after the third MMR dose who also had avidity results for the short-term immunity study (ie, participants who had low measles virus neutralizing antibody concentrations and a random sample of the remaining participants to represent the distribution of concentrations in the study population) [17]. Measles virus-specific IgG avidity was determined for IgG-positive specimens using an endpoint titration assay based on the Captia Measles IgG enzyme immunoassay (Trinity Biotech, Jamestown, New York) [25]. Results were interpreted as follows: low avidity if the end-titer avidity index (AI) \leq 30%, high avidity if AI \geq 70%, and intermediate if AI was between 30% and 70% upon retest. A low avidity result was interpreted as a primary immune response after vaccination with the third MMR dose and a failure to respond to previous doses; a high avidity result was interpreted as a matured IgG response; an intermediate avidity result was indicative of incomplete IgG maturation.

Rubella Virus Neutralizing Antibody

An immunocolorimetric neutralization assay was used to assess rubella virus neutralizing antibody concentrations as previously described [26], with some modifications for specimens collected at 5 and 9–11 years after the third MMR dose. Sera

were serially diluted in six 2-fold series beginning from 1:10 or 1:20. An in-house positive control from pooled human sera with low IgG titer (CDC Rubella Reference Standard enzyme immunoassay titer 21 IU/mL) and a commercial base matrix diluent from defibrinated human plasma (SeraCare, Milford, Massachusetts) were included with the tested sera in each plate to monitor the data quality. The endpoint was defined as a 50% reduction in infectivity as measured 3 days post-infection. Final neutralizing antibody concentrations (U/mL; the reciprocal of the 50% endpoint titer) were calculated by the Kärber method and normalized titer values from the in-house positive control were used to minimize data variation that was possibly introduced by the method used for the short-term study (Locally estimated scatterplot smoothing approach) [18]. Participants with rubella virus neutralizing antibody concentrations <10 U/mL were considered potentially susceptible to rubella infection and those with concentrations \geq 10 U/mL were considered protected against rubella infection [27, 28].

Statistical Analysis

Differences in characteristics between groups were assessed using χ^2 tests for categorical variables and Wilcoxon rank-sum test for \log_2 -transformed values. Data from participants who returned for either of the follow-up visits at 5 or 9–11 years after the third MMR dose were included in generalized estimating equation (GEE) models to estimate geometric mean concentrations (GMCs) and their corresponding Wald 95% confidence intervals (CIs) at 5, 9, and 11 years after vaccination with the third dose. The GEE models (PROC GENMOD) allowed for correlation (exchangeable) between antibody concentrations measured over time in the same individual, taking into consideration the time since receipt of the third dose. Time was modeled as time + time²; no other covariates were included in the model as they did not improve the goodness-of-fit by targeting the smallest QIC (quasilikelihood under the independence model criterion) statistic, were not statistically significant ($P > .05$), and did not change the time or time² coefficients by >15%. GMCs were reported as back-transformed values from the model that used \log_2 -transformed antibody concentration values. GMCs are predicted estimates, with the time points continuous and staggered across the data (ie, not all participants returned for follow-up at exactly 5, 9, or 11 years after the third MMR dose); therefore, statistical comparisons among time points was not possible. Reverse cumulative distribution curves were created to show the distribution of rubella and measles antibody concentrations over time. Data were analyzed using SAS 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

Of 665 participants who received a third MMR dose in 2009–2010, 405 (61%) and 304 (46%) were assessed at 5 and 9–11 years after the third dose, respectively (Figure 1). In 2019–2021,

Table 1. Characteristics of Study Population by Follow-up Visit and Number of Measles-Mumps-Rubella Vaccine Doses Received

Characteristic	3-Dose Recipients		2-Dose Recipients ^a
	5 y After the Third MMR Dose 2014–2016	9–11 y After the Third MMR Dose 2019–2021	24 y After the Second MMR Dose 2019–2021
No. of participants enrolled	405	304	20
Years since last MMR dose, median (range)	5.0 (4.6–5.9) ^b	9.2 (8.8–11.7) ^b	24.4 (24.3–27.2) ^c
Age at study visit, y, median (range)	26 (22–33)	31 (26–37)	29 (28–32)
Sex			
Male	157 (39)	107 (35)	6 (30)
Female	248 (61)	197 (65)	14 (70)
Non-Hispanic White	399 (99)	300 (99)	20 (100)
Age at first MMR dose			
12–15 mo	266 (66)	200 (66)	8 (40)
≥16 mo	139 (34)	104 (34)	12 (60)
Age at second MMR dose			
1–3 y	4 (1)	3 (1)	0
4–6 y	380 (94)	284 (93)	20 (100)
≥7 y	21 (5)	17 (6)	0
Age at third MMR dose			
18–22 y	289 (71)	217 (71)	NA
23–28 y	116 (29)	87 (29)	NA
Measles GMC (95% CI) before receipt of the third MMR dose, mIU/mL	727 (662–797)	747 (673–831)	NA
% potentially susceptible (<120 mIU/mL)	10 (3)	8 (3)	NA
Rubella GMC (95% CI) before receipt of the third MMR dose	40 (38–44)	41 (37–44)	NA
% potentially susceptible (<10 U/mL)	11 (3)	6 (2)	NA

Data are presented as No. (column percentage) unless otherwise noted.

Abbreviations: CI, confidence interval; GMC, geometric mean concentration; MMR, measles-mumps-rubella vaccine; NA, not applicable.

^aParticipants who received only 2 MMR doses; 4 were initially recruited in 2009–2010 but did not receive a third MMR dose, and 16 were newly recruited in the 2019–2021 from participants of a longitudinal study examining immunity of a second MMR dose (1994–2007).

^bTime from receipt of the third MMR dose to respective follow-up visit.

^cTime from receipt of the second MMR dose to respective follow-up visit.

20 participants who had previously received only 2 MMR doses were also enrolled and assessed. The characteristics of participants at each follow-up visit by number of MMR doses received are shown in Table 1. For 3-dose recipients, the follow-up visits occurred a median of 5.0 years (range, 4.6–5.9 years) and 9.2 years (range, 8.8–11.7 years) after receipt of the third MMR dose, and the median age was 26 years (range, 22–33 years) and 31 years (range, 26–37 years), respectively. Participants were predominately non-Hispanic White (≥99%) and female (61%–65%). For 2-dose recipients, enrollment occurred a median of 24.4 years (range, 24.3–27.2 years) after receipt of the second MMR dose, and the median age was 29 years (range, 28–32 years). No one reported potential exposure to or illness from measles or rubella, and 28% and 35% of participants reported travel outside the US since their last study visit, respectively, at 5 years and 9–11 years.

Measles

Measles Virus Neutralizing Antibody

Measles virus neutralizing antibody data were available for 404 and 304 participants who returned at 5 and 9–11 years

after the third MMR dose, respectively (Figure 1); 439 participants had data from at least 1 long-term follow-up visit. Among 3-dose recipients, the estimated measles virus neutralizing antibody GMC at 5 years was 428 mIU/mL (95% CI, 392–468 mIU/mL). GMC at 9 and 11 years was 360 mIU/mL (95% CI, 329–393 mIU/mL) and 381 mIU/mL (95% CI, 339–428 mIU/mL), respectively. The trend in GMCs from baseline through 11 years is shown in Figure 2A. The reverse cumulative distribution curves show the shift in measles virus neutralizing antibody levels during the long-term follow-up periods to levels lower than before receipt of the third dose (Figure 3A).

At approximately 5 and 9–11 years after the third dose, all participants had detectable measles neutralizing antibody levels (≥8 mIU/mL), though 11% and 10% of participants, respectively, were considered potentially susceptible to measles infection (Figure 3A). Participants who were considered potentially susceptible at 9–11 years had lower measles neutralizing antibody levels before receipt of the third dose than those considered protected against measles (GMC, 323 vs 1175 mIU/mL) and at each follow-up visit after receipt of the third MMR dose (1 month: 756 vs 1590 mIU/mL; 1 year: 384 vs

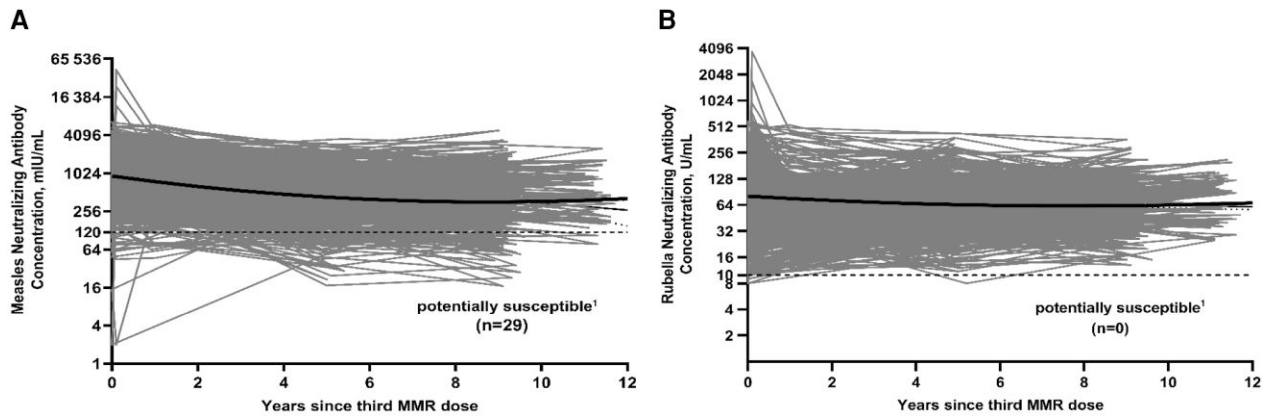


Figure 2. Measles (A, $n = 439$) and rubella (B, $n = 440$) virus neutralizing antibody concentrations among adults who received a third measles-mumps-rubella vaccine (MMR) dose in 2009–2010 and returned 5 and 9–11 years after receipt of the third dose. The geometric mean concentrations (GMCs) were estimated using generalized estimating equation model. The bold thick lines show the trend in GMC estimates for measles (left) and rubella (right) from before vaccination (year = 0) through 12 years after receipt of the third MMR dose. The light thin lines show the measles and rubella virus antibody concentrations over time for each participant. The dotted horizontal lines show concentrations <120 mIU/mL and <10 U/mL used as the susceptibility cutoff for measles and rubella, respectively. ¹Participants potentially susceptible at last follow-up visit (9–11 years after third MMR dose).

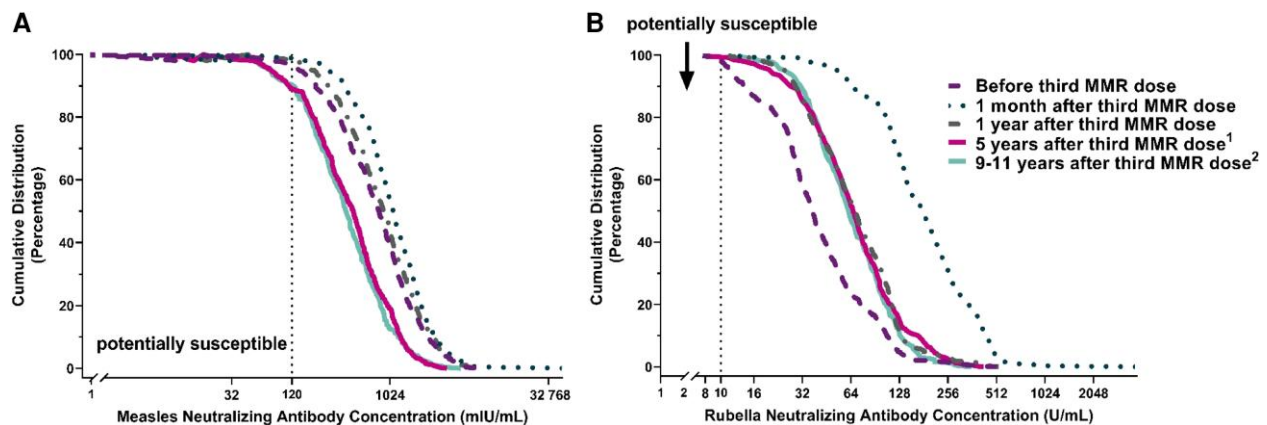


Figure 3. Reverse cumulative distribution curve by percentage of participants who received a third measles-mumps-rubella vaccine (MMR) dose and had measles (A) and rubella (B) virus neutralizing antibody concentrations at each study visit. The vertical dotted lines represent the cutoff for measles and rubella susceptibility. The horizontal axis represents antibody levels in a logarithmic scale and the vertical axis represents the percentage of participants having at least that level of antibody, ranging from 0% to 100%. ¹Range: 4.6–5.9 years. ²Range: 8.8–11.7 years.

1259 mIU/mL; 5 years: 296 vs 637 mIU/mL; 9–11 years: 70 vs 624 mIU/mL).

Among the 20 two-dose MMR recipients who returned approximately 24 years after vaccination, measles virus neutralizing antibody GMC was 391 mIU/mL (95% CI, 273–559 mIU/mL), with 5% considered potentially susceptible to measles infection (all had detectable antibody levels). GMCs among 2-dose recipients were comparable to similar-age adults who received 3 MMR doses ($P = .91$).

Measles Virus–Specific IgG Antibody Avidity

Of the 59 participants who were previously tested for measles virus–specific IgG antibody avidity before and up to 1 year after receipt of the third MMR dose [17], 33 (56%) returned 5 years after the third dose, and all had detectable IgG antibodies for evaluation of avidity. At the 5-year visit, measles virus–specific IgG antibody avidity was high for 32 of 33 (97%) participants tested, and 1 (3%) had intermediate IgG antibody avidity. All but 2 (6%) had neutralizing antibody concentrations considered protective against measles infection (Figure 4).

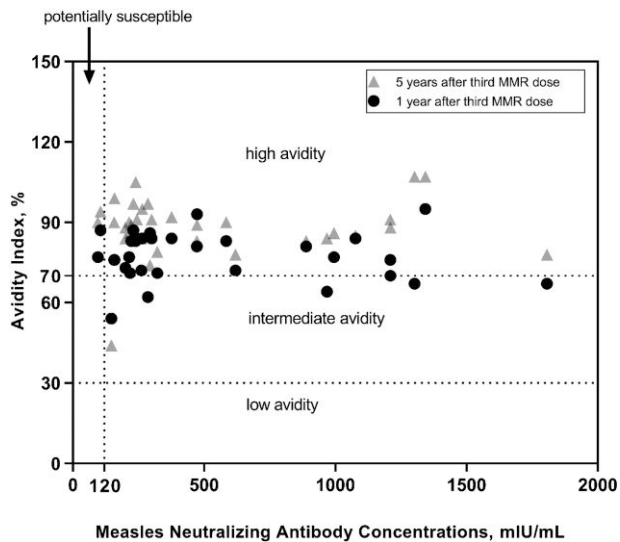


Figure 4. Measles virus neutralizing antibody concentrations relative to measles virus-specific immunoglobulin G avidity levels, according to end-titer avidity index, at 1 year (triangles) and 5 years (circles) after receipt of the third measles-mumps-rubella vaccine (MMR) dose ($n = 33$).

In comparison, 28 of the 33 participants (85%) had high measles virus-specific IgG antibody avidity, 5 (15%) had intermediate IgG antibody avidity at 1 year (Figure 4).

Rubella

Rubella Virus Neutralizing Antibody

Rubella virus neutralizing antibody data were available for 405 and 304 participants who returned 5 and 9–11 years after the third MMR dose, respectively (Figure 1); 440 participants had data from at least 1 long-term follow-up visit. Among 3-dose recipients, the estimated rubella virus neutralizing antibody GMCs remained stable throughout the long-term follow-up period: 64 U/mL (95% CI, 60–68 U/mL) at 5 years, 63 U/mL (95% CI, 59–66 U/mL) at 9 years, and 65 U/mL (95% CI, 60–71 U/mL) at 11 years. The trend in GMCs from baseline through 11 years is shown in Figure 2B. The reverse cumulative distribution curves show that the rubella virus antibody levels during the long-term follow-up periods remained higher than levels before receipt of the third dose and were similar to levels at 1 year after (Figure 3B). At approximately 5 and 9–11 years, 0.3% and 0% of participants were considered potentially susceptible to rubella infection, respectively (Figure 3B).

Rubella virus neutralizing antibody GMC among the 20 two-dose MMR recipients was 44 U/mL (95% CI, 33–58 U/mL), with 5% considered potentially susceptible to rubella infection approximately 24 years after receipt of the second dose. GMCs among 2-dose recipients were significantly lower than similar-age adults who received 3 MMR doses ($P < .0001$).

DISCUSSION

Among adults who received a third dose of MMR, we observed persistence of high neutralizing antibody levels against measles and rubella viruses through 11 years after vaccination. Rubella virus neutralizing antibody levels remained stable throughout the long-term follow-up period, while measles virus neutralizing antibody levels declined over time. Although all participants had detectable measles neutralizing antibody levels, 10% of 3-dose recipients were considered potentially susceptible to measles infection by 9–11 years after receipt of the third dose.

The decline in measles virus neutralizing antibody levels after a third MMR dose observed in our study was not surprising. Several longitudinal studies have shown that measles virus antibodies slowly wane, and the percentage of persons becoming potentially susceptible increase as the time since receipt of the second MMR dose increases [7–11]. The reported average rate of decline after the second dose ranged from 3% to 15% per year [7, 8, 10, 13], and the rate of decline may be substantially lower with longer follow-up (eg, >8 years) [10]. Measles virus antibody levels also declined with time among adults who received a third dose of MMR in the Netherlands, though antibody levels persisted for up to 3 years after the third dose and remained significantly higher than levels at baseline [14]. In our study, measles virus neutralizing antibody levels beyond 5 years after receipt of the third dose were lower than levels before receipt of the third MMR dose. Although measles antibody levels were below baseline during the long-term follow-up period, they remained well above the accepted susceptibility threshold of 120 mIU/mL in 90% of participants. Furthermore, antibody levels among the 3-dose recipients were similar to levels among a small sample of similar-age adults who received their second MMR dose approximately 24 years prior.

The 10% of 3-dose recipients considered potentially susceptible to measles by 9–11 years after vaccination in our study is higher than the 3% for the same group before receipt of the third dose and the 5% reported 5 to 10 years after the second dose [7, 10]. The low level of measles neutralizing antibody levels may not necessarily indicate susceptibility among these persons. Both humoral and cellular immunity play a role in protection from measles. Immunological memory likely persists in many of these persons. During an outbreak in Senegal, no vaccinated children with low levels of measles neutralizing antibody (40–125 mIU/mL) exposed within the household were reported to have developed measles, suggesting sufficient cellular immunity to provide protection despite low antibody levels [29]. Furthermore, T-cell responses to measles vaccination do not appear to wane and can persist at least 1 to 5 years in children [30]. Additionally, participants who were considered potentially susceptible at 9–11 years after the third dose had consistently lower measles neutralizing antibody

levels at any time point before the 9–11 years assessment, starting with before receipt of the second dose, potentially indicating an inability to mount a sufficient humoral immune response. Additional studies examining persistence of cellular immunity in adults, and studies with longer follow-up to confirm the declining trend in neutralizing antibody titers and increased susceptibility with increased time since vaccination among those who have received 2 and 3 MMR doses are needed. Taken together, short- and long-term immunity data do not currently suggest an advantage of a third MMR dose for seroprotection against measles [17].

In contrast to measles and previous longitudinal assessments of rubella antibody levels after vaccination [8, 10, 12, 13], our study found no evidence of waning for rubella. Among 2-dose recipients in Olmstead County, Minnesota, rubella antibody levels were stably maintained up to 17 years after vaccination despite significant declines in antibody titers with time [31]. Similarly, children who received a second MMR dose had elevated rubella virus antibody levels that persisted for at least 12 years after vaccination, even when antibody levels were significantly lower than peak levels after vaccination [12]. In our study, among adults who received a third dose, rubella virus neutralization antibody levels remained high, above levels prior to vaccination with the third MMR dose, and were stable from 1 year through 11 years after vaccination. Furthermore, rubella virus neutralizing antibody concentrations were significantly higher among 3-dose recipients than similar aged 2-dose recipients in our study. Although there is little substantial advantage of a third MMR dose for seroprotection against rubella, it provides reassurance that women of childbearing age who receive a third MMR dose (eg, because they have rubella-specific IgG levels that were not positive) likely have antibody levels that will persist through their peak reproductive years, supporting the current vaccination recommendations for women of childbearing age to receive a maximum of 3 MMR doses without subsequent retesting for serologic evidence of rubella immunity [1].

Our study had several limitations. First, study participants were mostly non-Hispanic White and were recruited from predominantly rural central Wisconsin, which may not be representative of the general US population. Second, some study participants were lost to follow-up. For the follow-up visit at 5 years after the third dose, 62% of those eligible returned, and by the visit at 9–11 years after the third dose, less than half (47%) of eligible participants returned to provide specimens for serologic testing. However, there were >300 participants at each study visit, and baseline demographic and serologic characteristics of those who returned were similar to those of the original cohort [7, 12, 17]. Third, testing for measles and rubella virus neutralizing antibodies for this long-term evaluation occurred in a different laboratory than the one used for the short-term evaluation, which could potentially

limit comparison of the short- and long-term visits. However, both assays were validated against laboratory testing standards, and results were similar (data not shown). Fourth, our sample size of similar-age 2-dose recipients used as a comparison group was small and the antibody levels soon after the second dose were not available for comparison. However, no significant differences in characteristics examined were found between this group and the 3-dose recipients. Future studies should include a larger sample size of similar-age adults with 2 MMR doses to compare antibody levels and rate of decline over time with 3-dose recipients. Last, we did not examine cell-mediated immunity that could provide additional information on the persistence of immunity after the third dose and protection from measles infection.

Third doses of MMR will continue to be administered to adults for various reasons. The modest boost in measles virus neutralizing antibody levels after receipt of the third MMR dose was short-lived [17], and long-term immune response for measles did not appear to be affected by the additional dose. In contrast, the boost in rubella virus neutralizing antibody levels after receipt of the third MMR dose was sustained through 11 years after vaccination [18] and was higher than levels among similar-age 2-dose recipients.

Notes

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Patient consent. Participants provided informed consent before enrollment at each follow-up visit. The study was approved by the institutional review boards at MCRI and CDC and were conducted consistent with applicable federal law and CDC policy (45 Code of Federal Regulations [C.F.R.] part 46; 21 C.F.R. part 56).

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

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