

Persistence of Measles Antibodies After 2 Doses of Measles Vaccine in a Postelimination Environment

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Objective: To evaluate the persistence of measles antibodies after 2 doses of measles vaccine in a setting where exposure to wild-type measles was unlikely. Measles was declared eliminated from the United States in 2000, an achievement attributed to effective implementation of a routine 2-dose vaccination policy. Some have questioned whether measles transmission could resume if immunity wanes in the absence of boosting from wild-type measles.

Design: Prospective, observational, volunteer cohort study.

Setting: Rural Wisconsin health maintenance organization.

Participants: Children who received the second measles vaccine dose at kindergarten (aged 4-6 years) or middle school (aged 10-12 years) in 1994 or 1995. Serum samples were collected periodically during a 10-year period for the kindergarten group and a 5-year period for the middle school group.

Intervention: Second dose of measles vaccine.

Main Outcome Measure: Measles antibody levels were assessed by plaque-reduction neutralization: titers less than 8 mIU/mL were considered seronegative and suggestive of susceptibility to measles, and titers of 120 mIU/mL or less were considered low and suggestive of potential susceptibility.

Results: During the study period, no measles was reported in the study area. Voluntary attrition reduced the study population from 621 at enrollment to 364 (58.6%) by study end. Before the second dose, 3.1% (19/621) had low titers, of whom 74% (14/19) were antibody-negative, with geometric mean titers being significantly higher in kindergarteners (1559 mIU/mL) than in middle schoolers (757 mIU/mL) and rates of negativity significantly lower (1.0% [3/312] vs 3.6% [11/309]). One month after the second dose, 0.2% (1/612) had low titers and none was seronegative, with geometric mean titers being significantly higher in kindergarteners (2814 mIU/mL) than in middle schoolers (1672 mIU/mL). By study end, 4.9% (18/364) had low titers and none was seronegative, with no significant difference in geometric mean titers between kindergarteners (641 mIU/mL) and middle schoolers (737 mIU/mL) when both groups were aged 15 years. Projections suggest that the proportion of persons with low antibody levels may increase over time.

Conclusions: Measles antibody persisted in all vaccinees available for follow-up 10 years after a second dose of vaccine, with no seronegative results detected. Declining titers suggest the need for vigilance in ensuring disease protection for the vaccinated population.

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BEFORE LICENSURE OF MEASLES vaccine in 1963, approximately 4 million cases, 50 000 hospitalizations, and 500 deaths due to measles occurred annually in the United States.¹ Within 20 years of vaccine introduction, measles incidence had been reduced by 99%, but transmission continued, particularly among schoolchildren who had received only 1 dose of vaccine.¹ In 1989, facing a nationwide measles resurgence, the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics recommended that schoolchildren receive a second dose of measles-mumps-rubella vaccine (MMR) to provide protection to those who had an inadequate response to the first dose.^{2,3} Since

then, the number of MMR doses administered annually has been enough to provide 2 doses to each child in the US birth cohort, plus catch-up doses to 4 million others.⁴ By 1993, viral transmission was interrupted⁵ and, by 2000, measles was declared eliminated in the United States,⁶ a historic achievement attributed to effective implementation of a routine 2-dose measles vaccination policy.⁷

Childhood vaccination levels remain high,⁸ but imported disease remains a threat because approximately 40 million measles cases occur globally each year.⁹ Many studies have suggested that vaccine-induced immunity is persistent, perhaps even lifelong, but most were performed in an era when boosting from wild-type virus was common.¹⁰⁻¹⁴ Some investigators

Table 1. Study Design and Subject Retention

Age, y	MMR2 in Kindergarten				MMR2 in Middle School			
	Serum No.	Time From MMR2	Year Span	Subjects, No. (%)*	Serum No.	Time From MMR2	Year Span	Subjects, No. (%)*
5	1	Before	1994-1995	312 (100.0)				
	2	1 mo	1994-1995	304 (97.4)				
	3	6 mo	1994-1995	302 (96.8)				
7	4	2 y	1996-1997	243 (77.9)				
10	5	5 y	1999-2000	174 (55.8)	1	Before	1994-1995	309 (100.0)
					2	1 mo	1994-1995	308 (99.7)
					3	6 mo	1994-1995	306 (99.0)
12	6	7 y	2001-2002	161 (51.6)	4	2 y	1996-1997	266 (86.1)
15	7	10 y	2004-2005	154 (49.4)	5	5 y	1999-2000	210 (68.0)

Abbreviation: MMR2, second dose of measles-mumps-rubella vaccine.
*Percentage of originally enrolled cohort.

have raised concerns that, in the absence of such boosting, waning immunity may produce a population of susceptible persons sufficient to sustain renewed measles transmission.¹⁵⁻²¹ Because measles tends to be more severe clinically among adults,¹⁰ progressive waning immunity might have important clinical and public health consequences.

In 1994, the Centers for Disease Control and Prevention began a longitudinal study of the persistence of measles antibody levels comparing 2 different measles second-dose vaccination schedules. At the time, based on then-divergent ACIP and American Academy of Pediatrics recommendations,^{2,3} some states had passed laws requiring the second dose for kindergarten entry and others for middle school entry, although ultimately all required it for school entry at some age. Subsequently, ACIP and the American Academy of Pediatrics agreed on a kindergarten recommendation,^{22,23} but many states continued with their original legal requirements. We report the findings of this longitudinal study.

METHODS

The study was conducted to evaluate short- and long-term antibody response after a second dose of MMR vaccine (MMR2) in a setting where exposure to wild-type measles was unlikely, and to compare schedules in which MMR2 was administered at kindergarten vs middle school entry. We hypothesized that measles antibody levels would not be significantly lower at high school age for children who received the second dose of vaccine in kindergarten than for those who received it in middle school.

STUDY PARTICIPANTS

The study population was drawn from patients of Marshfield Clinic, the principal health care provider for a rural area of Wisconsin with a low incidence of reported measles. The clinic has a longitudinally stable patient population with a low rate of utilization of outside care.

The state of Wisconsin had enacted a law in 1990 requiring MMR2 for children entering kindergarten and middle school. The computerized files of Marshfield Clinic were reviewed to identify 2 groups of MMR2-eligible children: those in kinder-

garten (4-6 years old) and those in middle school (10-12 years old). Families were contacted and information was obtained about the mother's date of birth, child's date of birth, documented dates of all vaccinations, sex, race-ethnicity as declared by the family, history of measles-mumps-rubella disease or exposure, and current state of health. The date of the first administration of MMR (MMR1) was verified by provider record check, and children who did not receive MMR1 between 12 and 24 months of age were excluded. Candidate study subjects were also excluded if they had (1) previously had either measles, mumps, or rubella, since different parts of the study evaluated immune response to each antigen; (2) lived in the same household with anyone who had had these diseases during the subject's lifetime; (3) previously received any component of MMR vaccine other than as specified herein; (4) received any other vaccinations within 30 days before the scheduled date of MMR2 administration; (5) any contraindication to MMR vaccination according to ACIP recommendations²²; or (6) any condition likely to impair immune response to MMR vaccine according to ACIP recommendations.²² Parents of study subjects were provided with informed permission materials, and middle schoolchildren were additionally provided with informed assent materials. The study was approved by the Human Subjects Protection offices of Marshfield Clinic, the Centers for Disease Control and Prevention, and the Food and Drug Administration.

STUDY DESIGN AND METHODS

Serum samples were obtained from enrolled children, and the second dose (M-M-R II; Merck & Co Inc, Whitehouse Station, NJ) was administered less than 72 hours thereafter, along with any other vaccines for which the child was eligible. Adverse events in the month after vaccination were examined, as previously reported.²⁴ Postvaccination serum samples were drawn at intervals permitting comparisons of the 2 groups at similar ages (**Table 1**). At each specimen collection, families were questioned concerning measles exposures, vaccinations, and other health events.

Measles antibody levels were evaluated by means of the plaque-reduction neutralization (PRN) test, as previously described.²⁵ Fourfold serial dilutions of serum were tested in duplicate starting at 1:8 and ending at 1:8192 and run in parallel with the Second World Health Organization International Standard Reference Serum (66/202). Serum samples with reciprocal titers of less than 8 or greater than 8192 were assigned values of 4 and 16 400, respectively. Geometric mean titers were

Table 2. Study Population Characteristics

Characteristic	Group	
	Kindergarten (n = 312)	Middle School (n = 309)
Sex, No. (%) F	153 (49.0)	150 (48.5)
Race/ethnicity, No. (%) non-Hispanic white	305 (97.8)	307 (99.4)
Mother's birth year, median (range)*†	1961 (1946-1972)	1957 (1940-1967)
Age at MMR1, median (range), mo	15.6 (12.8-24.7)	15.7 (14.1-24.5)
Time between MMR1 and MMR2, median (range), y†	3.7 (2.4-4.8)	9.8 (8.4-11.2)
Age at MMR2, median (range), y†	5.1 (4.2-6.1)	11.2 (10.1-12.5)
Receipt of other immunizations with MMR2, No. (%)†	222 (71.2)	1 (0.3)

Abbreviations: MMR1 and MMR2, first and second doses of measles-mumps-rubella vaccine, respectively.

*Birth year of biological mother could not be ascertained for 15 children (5 in the kindergarten group and 10 in the middle school group) who lived with other persons.

†Differences between the kindergarten and middle school groups were significant at $P < .001$ for 4 characteristics (mother's birth year, time between MMR1 and MMR2, age at MMR2, and receipt of other immunizations with MMR2). Differences were not significant at $P < .05$ for other characteristics (sex, race, and age at MMR1).

calculated as log-transformed reciprocal neutralizing antibody titers and reported as back-transformed titers standardized against the Second World Health Organization reference serum, with 1:8 corresponding to 8 mIU/mL. To ensure comparability of results for assays performed during the 10-year course of the study, an assay was considered valid only if the end point titer measured for the World Health Organization reference serum did not vary by more than 20% from the assigned titer of 1:5000. Each serum drawn 1 month after MMR2 administration was also evaluated for anti-measles IgM by enzyme immunoassay, as previously described.²⁶ Serum samples with an optical density index of 1.0 or greater were considered positive; those at 0.5 to 0.9 were considered indeterminate.

On the basis of studies comparing preexisting PRN titers with subsequent measles attack rates,^{27,28} serum samples were assigned to 1 of 4 categories of antibody level: (1) negative (<8 mIU/mL), susceptible to infection and disease; (2) low (8-120 mIU/mL), potentially susceptible to infection and disease; (3) medium (121-900 mIU/mL), potentially susceptible to infection but not to disease; and (4) high (>900 mIU/mL), not susceptible to infection or disease. Serum samples were also dichotomized as potentially susceptible (≤ 120 mIU/mL) and not susceptible (>120 mIU/mL). The following potential risk factors for antibody levels were examined: sex, mother's birth year, age at MMR1, time between MMR1 and MMR2, receipt of other vaccinations with MMR2, and (for post-MMR2 serum samples) pre-MMR2 titer levels.

STATISTICAL AND MODELING METHODS

To detect a difference in potential susceptibility of 5% vs 15% between the 2 study groups, with 80% power and 95% confidence intervals, a sample size of 300 was estimated. Assuming 50% attrition during the 10-year study, an enrollment goal of 600 was set. To evaluate the potential impact of attrition on study findings, we compared risk factor characteristics and antibody levels for those initially enrolled with those of the subset who completed the study. In bivariate comparisons, the Pearson χ^2 test was used for categorical variables, the row-mean-scores/Cochran-Mantel-Hansel test for ordinal variables, and the Wilcoxon rank sum for continuous variables. For testing the association between continuous variables, multiple linear regression was used.

To estimate future antibody trends, we restricted analysis to the kindergarten group, for whom we had 10 years' data and whose dosing schedule followed current US policy. We deter-

mined the 25th percentile, median, and 75th percentile of titers for each serum collection, then fitted linear regression models to the natural logs of these quantiles, and projected future values of these percentiles. A linear regression model was also fitted to the raw scatter of log_e titers to predict the mean log_e titer beyond the last collection. The predicted mean log_e titers and mean squared error estimated from this model were used as means and variances, respectively, of normal distributions for projecting the future proportions of the cohort with low and negative titers. This model was previously used by Woolhouse et al²⁹ for examining vaccination-induced protection against foot-and-mouth disease. Because no postvaccination neutralizing titers were below the limit of detection in our study, it was not necessary to use the more complicated mixture model described by Moulton and Halsey³⁰ for regression analysis of antibody response to measles vaccine or that used by Mossong et al^{18,31} for projecting future measles PRN titers of 120 mIU/mL or less in the absence of wild-type measles boosting, both of which take into account censored observations arising from the lower limit of antibody assays. Confidence intervals around our predicted proportions of the population with lower than protective antibody titers were obtained by standard statistical methods. As an internal check, we examined how closely the model's "back-estimate" of the prevaccination antibody levels of the middle schoolers when they were in kindergarten approximated the measured prevaccination levels of the kindergarten study group: the predicted geometric mean titer (1626 mIU/mL) differed by 4% from the measured geometric mean titer (1559 mIU/mL).

RESULTS

A total of 621 children were enrolled, of whom 608 (97.9%) provided serum samples through the first 3 collections (Table 1). Thereafter, attrition reduced the study population to 364 (58.6%) by the final collection. Overall and within each group, the 364 children who completed the study did not differ significantly from the initially enrolled 621 for available titers or any risk characteristic.

Reflecting the rural Midwestern source population, 98.6% (612/621) of the overall study population was non-Hispanic white (Table 2), with no significant difference between the groups. Middle schoolers' mothers

were born significantly earlier than kindergarteners'. Specifically more were born before 1957 (presumed immune from wild-type virus under US policy²²): 43.8% (131/299) vs 14.3% (44/307); $P < .001$. Per study protocol, all children received MMR1 between 12 and 24 months of age, most within 60 days of 15 months of age, with no significant difference between groups.

POTENTIAL MEASLES EXPOSURES

The 7 counties surrounding the clinic (2000 population, 364 187)³² reported 41 confirmed cases of measles to the Centers for Disease Control and Prevention from 1985 (the first year for which county-specific data are available) until the start of the study in 1994. Subjects' birth years ranged from 1981 to 1991, so local exposure to measles was possible before the study start, although none was reported by study families. During the study period (1994-2005), no measles cases were reported in the 7 counties, and no family reported measles exposure. According to clinic records, no study subject was diagnosed as having measles or received additional measles vaccinations from birth through 2005. To assess the extent to which unreported measles exposures may have occurred among the study population, we looked for 4-fold titer increases in drawn serum samples starting 6 months after MMR2 through the end of the study. Among 1208 serum pairs, one 4-fold rise was detected. The child's family denied any exposure to measles, foreign travel, or repeat measles vaccinations.

TITERS BEFORE AND AFTER MMR2

Before the second dose, the majority of both groups had high titers, and the proportion of potential susceptible individuals was small (3.1% [19/621]), but 74% (14/19) of these were antibody-negative (**Figure 1**). Compared with middle schoolers, kindergarteners had higher titers (geometric mean titer, 1559 vs 757 mIU/mL; $P < .001$), fewer potentially susceptible individuals (1.0% [3/312] vs 4.9% [15/309]; $P = .002$), and fewer negative samples (1.0% [3/312] vs 3.6% [11/309]; $P = .03$).

One month after MMR2, titers significantly increased for each study group, but beyond 6 months titers were not significantly different from pre-MMR2 levels (Figure 1). Similarly, a 4-fold rise in titers was observed for 11.6% (71/612) of the study population 1 month after MMR2, but this declined to 3.6% (22/608) by 6 months and 1.3% (2/154) by 10 years. All 14 children who were seronegative (< 8 mIU/mL) before MMR2 maintained titers greater than 120 mIU/mL at every post-MMR2 serum collection. Of these, 6 (43%) had positive and 5 (36%) had indeterminate IgM responses. Titers for the 5 children with low prevaccination antibody levels (8-120 mIU/mL) increased less than did titers for the 14 children who were seronegative (range of 6-month titers, 104-323 vs 427-16 400 mIU/mL), but all 5 achieved titers greater than 120 mIU/mL at their last serum collection. None of the 5 had a positive or indeterminate IgM response. For the 602 children who had medium or high antibody levels before MMR2, titers increased significantly at 1 month but returned to pre-MMR2 levels

by 6 months, at which point only 1.0% (6/583) had titers 4-fold higher than at baseline. Of these 602 children, 1 (0.2%) had a positive IgM response and 4 (0.7%) had an indeterminate response. Kindergarteners had significantly higher titers than middle schoolers both 1 month and 6 months after MMR2.

Of 2428 post-MMR2 specimens tested, 32 (1.32%) showed potential susceptibility (≤ 120 mIU/mL), but none was negative (< 8 mIU/mL). Titers fell significantly over time for the study population overall and, by the final collection, 4.7% (18/382) of children were potentially susceptible, not significantly different from the pre-MMR2 proportion (3.1% [19/621]), though none was negative. Of those who were potentially susceptible at the last serum collection, none had been potentially susceptible before MMR2. At each serum collection, kindergarteners maintained significantly higher titers than middle schoolers but, at equivalent post-MMR2 ages (12 and 15 years), antibody levels and rates of susceptibility were not significantly different between the groups.

RISK FACTORS FOR MEASLES ANTIBODY LEVELS

For pre-MMR2 titers, shorter time since MMR1 was the only factor significantly associated with higher titers ($R^2 = 0.09$, $P < .001$). Although explaining less than 10% of titer variability, this factor was sufficient to explain the higher titers in kindergarteners than middle schoolers. For each post-MMR2 titer, the dominant factor was higher pre-MMR2 titers ($R^2 = 0.215-0.318$, $P < .001$) (**Figure 2**). Of the 18 children who were potentially susceptible on the final serum collection, 13 (72%) had been in the lowest quartile of titers before MMR2. With each successive collection, length of time since MMR1 played a diminishing role in post-MMR2 antibody levels, ultimately adding only about 0.1% to the value of a multivariate linear regression model. No other evaluated factor played a significant role in post-MMR2 antibody levels.

PROJECTED ANTIBODY LEVELS

Projection of future antibody levels in the kindergarten group suggested a continued slow decline in titers, with an increase in the proportion potentially susceptible (≤ 120 mIU/mL) reaching 33% by 20 years after MMR2 (**Figure 3**). However, the proportion seronegative (< 8 mIU/mL) was not projected to reach 1% until 30 years after MMR2.

COMMENT

In summary, we found that, in a population of children who had received 2 doses of measles vaccine at ages and intervals consistent with US policy and who were unlikely to have been exposed to wild-type measles, potential susceptibility rates were low for as long as 10 years after the second dose. These findings are consistent with low rates of 2-dose vaccine failure during US outbreaks³³⁻³⁵ and cross-sectional serosurveys indicating high rates of immunity across multiple US age strata.³⁶ How-

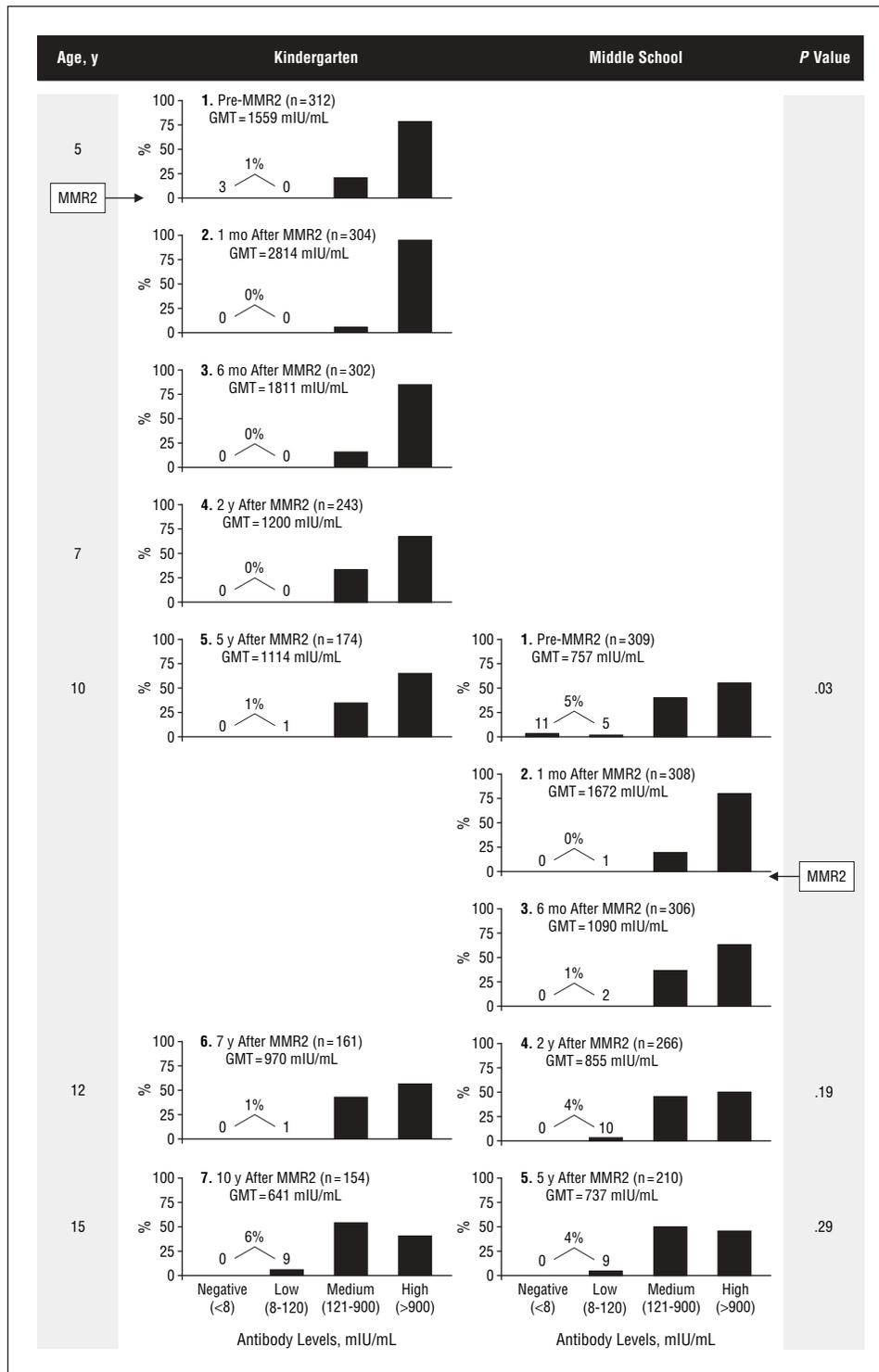


Figure 1. Changing distribution of antibody levels. Numerals above bars for the 2 lower antibody categories (negative and low) indicate the number of children in each category; the percentage above these numerals represents the proportion potentially susceptible (titers, ≤ 120 mIU/mL). The boldface numeral in the top left corner of each graph represents the serum collection; MMR2, second measles-mumps-rubella vaccination; n, the population providing serum samples at that collection; and GMT, geometric mean titer for that collection. P values are from the Wilcoxon rank sum test indicating the difference between the 2 groups in antibody titers at equivalent ages.

ever, the progressive decline in antibody levels suggests the need for continued vigilance in ensuring disease protection for the vaccinated population.

Two prospective studies^{27,28} have examined the relationship between low PRN titers and risk of measles disease. On a US college campus where a blood drive had occurred before a measles outbreak, 7 of 8 students with PRN titers of 16 to 120 mIU/mL acquired measles, compared with 0 of 71 with titers greater than 120 mIU/mL.²⁷ Dur-

ing a vaccine trial in Senegal, 13 of 36 children with titers of 40 to 125 mIU/mL acquired measles, compared with 7 of 258 of those with titers greater than 125 mIU/mL.²⁸ These studies suggest that low antibody levels may not be protective against measles disease, and the 120-mIU/mL threshold of potential susceptibility used in our study has been used in previous studies modeling projections of vaccine-induced immunity in the absence of wild-type measles boosting.¹⁸

A rise in the proportion of persons with low antibody levels suggests an increase in potential susceptibility, but low titers are unlikely to represent the same risk of illness or viral transmission as absent antibodies.^{28,37-39} In our study, none of the children with low titers had positive or even indeterminate IgM responses to MMR2, in contrast to the majority of those with negative titers, suggesting that those with low titers may generate an anamnestic response to wild-type virus, consistent with previous studies.³⁷⁻³⁹ If ongoing viral transmission requires that a substantial portion of the population be antibody-negative, our data suggest that such a situation may be several decades away. Furthermore, as demonstrated by Ward et al³⁷ and Gans et al,^{40,41} cell-mediated immunity plays an important role in resistance to measles infection, an issue we did not address. This is an area in which large-scale prospective studies are needed to provide reliable and quantifiable population-based indicators of cell-mediated protection from measles disease. Such studies would assist clinicians and public health policymakers to determine the relative importance of measles-specific T cells to protection as they encounter an expanding number of persons with low, indeterminate, or undetectable measles antibody levels.

In our study, intrinsic regulatory processes appeared to play an important role in maintenance of specific antibody levels. Persons with starting antibody levels higher than those of their peers tended to be boosted higher and stay higher over time. These data imply a preferred steady state of antibody production for each individual, findings consistent with those of St Sauver et al⁴² and Poland and colleagues⁴³ demonstrating an important role for genetic factors in measles immunity.

For both study groups, MMR2 immediately increased titers and virtually eliminated potential susceptibility. Although the titer increase lasted no longer than 6 months, rates of potential susceptibility did not return to prevaccination levels until 5 to 10 years later, and children with negative antibody levels were not detected at study end. At each collection, kindergarteners tended to have higher titers than middle schoolers but, for equivalent post-MMR2 ages, antibody levels were not significantly different. While these data do not suggest a dramatic advantage for either dosing schedule in the high school years, those who received the second dose at kindergarten were protected through the primary school years.

Our findings should be interpreted cautiously. Study subjects were not representative of the US childhood population: all came from a rural environment, almost all were non-Hispanic white, all were in good health, and all received MMR doses at recommended ages. Immunocompromised and other children who might not receive, or respond to, MMR were excluded from our study, and these children may form a growing and important group of susceptible individuals in the future. Attrition reduced the kindergarten group by more than half and the middle school group by almost a third. Our categorization of antibody levels is based primarily on 2 studies. We did not assess cellular-mediated responses to measles virus, and low titers are not necessarily equivalent to lack of immunity.

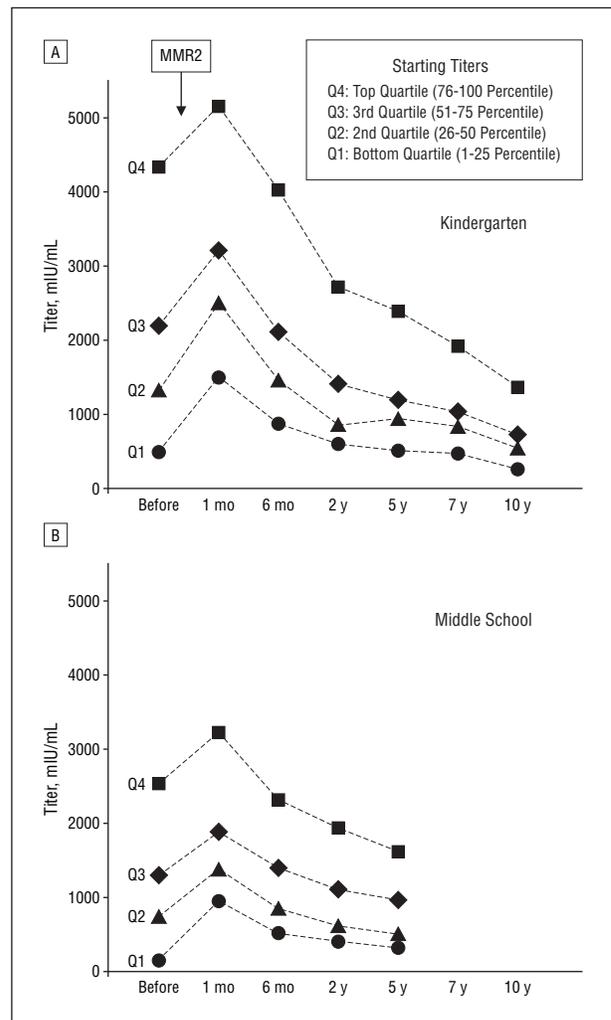


Figure 2. Serial antibody levels by starting titer in the kindergarten group (A) and the middle school group (B). Serum collections on the x-axis are not corrected for time scale. The population was divided into 4 cohorts based on quartile (Q) of antibody level before second measles-mumps-rubella vaccination (MMR2). Lines represent geometric mean titers for each cohort at each serum collection.

Projecting antibody levels decades into the future is an inherently speculative enterprise, in which small changes in slope can result in large alterations in predicted titers. In the absence of antigenic stimulation, titers can be expected to decline, but the rate of decline may flatten out, producing a steady state of long-term protection rather than an increasing number of susceptible individuals. To date, 2-dose failure has been relatively rare in US outbreaks, most which have been associated with 1-dose failure or failure to vaccinate.³³⁻³⁵ However, because elimination of indigenous measles was only declared in 2000, it may be some time before the majority of the US population has measles immunity that is attributable to vaccine alone. The resurgence of pertussis among teenagers and young adults requiring addition of an adolescent booster dose⁴⁴ and recent outbreaks of mumps among college students who had received 2 doses of MMR⁴⁵ suggest that it may be risky to discount the potential threat of diseases that appear on the verge of extinction because of high vaccination levels among toddlers.

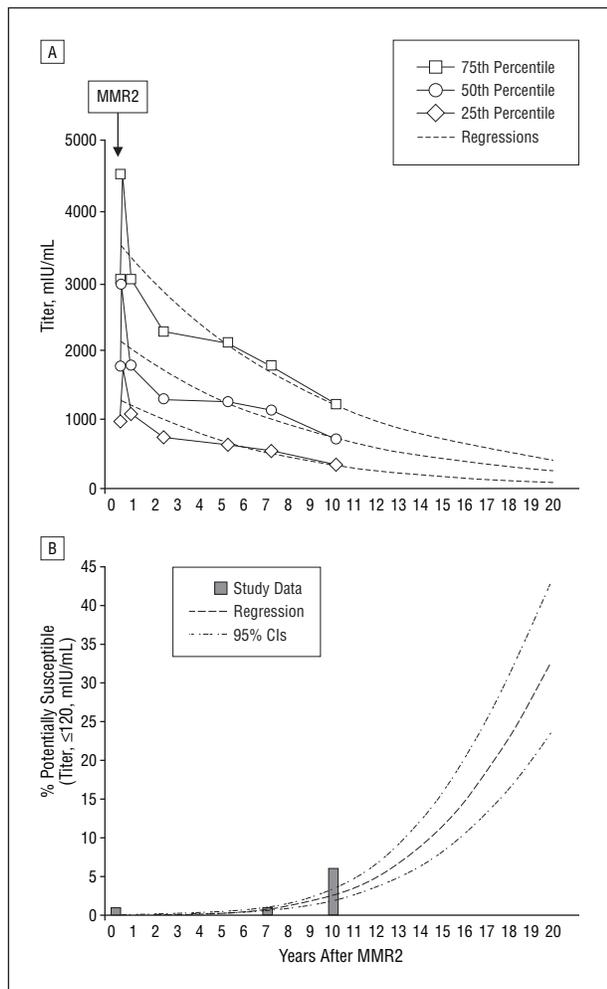


Figure 3. Projected antibody levels. A, Titers in the kindergarten group. B, Percentage potentially susceptible in the kindergarten group. The percentage seronegative (titer, <8 mIU/mL) is not shown because it was predicted to be less than 1% through 20 years after second measles-mumps-rubella vaccination (MMR2). CI indicates confidence interval.

We believe our study demonstrates that the US routine 2-dose measles vaccination strategy can produce high rates of seropositivity that persist for as long as 10 years after the second dose, even in the absence of wild-type virus boosting. Nonetheless, cessation of disease transmission can produce complacency. Maintenance of measles elimination will require continued high rates of 2-dose vaccination,^{7,46} vigilance in monitoring population-based immunity levels,⁴⁷ and reduction in the risk of imported disease through support to other nations in their efforts to control or eliminate measles.⁴⁸

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The oldest medical text extant anywhere is a cuneiform tablet from Mesopotamia. The most ancient known Egyptian medical writings date from a later period, but they refer back to texts far older. Most important among the more ancient treatises were: *Book on the Vessels of the Heart*; *The Physician's Secret: Knowledge of the Movement of the Heart and Knowledge of the Heart*; and *Collection on the Expelling of the Wehedu* (a toxic principle in the body).

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