

Measles in Children Vaccinated With 2 Doses of MMR



WHAT'S KNOWN ON THIS SUBJECT: School outbreak investigation in Quebec, Canada suggested that adolescents previously vaccinated with 2 doses of measles vaccine beginning at 12 months of age were at greater measles risk than those whose first dose was given at ≥ 15 months of age.



WHAT THIS STUDY ADDS: Greater measles risk among earlier first-of-2-dose vaccine recipients was replicated as a generalized provincial finding during the 2011 epidemic in Quebec, Canada. The mechanism remains unknown, but the findings warrant additional evaluation in the context of measles elimination efforts.

abstract



OBJECTIVE: A previous measles outbreak investigation in a high school in Quebec, Canada identified 2-dose vaccine effectiveness of 94%. The risk of measles in 2-dose recipients was significantly higher (2–4 times) when measles vaccine was first administered at 12 versus ≥ 15 months of age, with no significant effect of the age at second dose. Generalizability of this association was also assessed in the expanded provincial data set of notified cases.

METHODS: This matched case–control study included only 2-dose recipients. All confirmed (laboratory or epidemiologically linked) cases in patients aged 5 to 17 years were included. Each case was matched to 5 controls.

RESULTS: A total of 102 cases and 510 controls were included; 89% of cases were in patients 13 to 17 years old. When the first dose was administered at 12 to 13 months compared with ≥ 15 months of age, the risk of measles in participants outside the outbreak school was 6 times higher (95% confidence interval, 1.33–29.3) and was 5.2 times higher (95% confidence interval, 1.91–14.3) in the pooled estimate (participants from the outbreak school + outside that school).

CONCLUSIONS: A significantly greater risk of measles among 2-dose recipients whose first dose was given at 12 to 13 months rather than ≥ 15 months of age is confirmed in the larger Quebec data set. The mechanism remains unknown, but vaccine failures in 2-dose recipients could have substantial implications for measles elimination efforts through 2-dose vaccination. The optimal age at first dose may warrant additional evaluation. *Pediatrics* 2013;132:e1126–e1133

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KEY WORDS

measles, vaccine effectiveness

ABBREVIATIONS

CI—confidence interval

MMR—measles–mumps–rubella

OR—odds ratio

VE—vaccine effectiveness

Ms Defay conceptualized and designed the study, carried out data extraction and statistical analyses, contributed to the interpretation of data, and drafted the initial manuscript; Drs De Serres and Skowronski conceptualized and designed the study, contributed to the analysis and interpretation of data, and critically reviewed the manuscript for important intellectual content; Ms Boulianne conceptualized and designed the study, coordinated and supervised data collection and extraction, and critically reviewed the manuscript for important intellectual content; Ms Ouakki contributed to the data extraction and statistical analyses and critically reviewed the manuscript for important intellectual content; Drs Landry, Brousseau, and Ward conceptualized and designed the study and critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted.

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When the live attenuated measles vaccine was developed in the 1950s,¹ it was initially recommended for administration at 9 months. This was soon changed when greater efficacy was observed with older age at vaccination because of concern about possible interference from residual maternal measles antibody.² Because maternal antibodies wane over time, interference diminished with age, and protection increased with older age at first dose, plateauing at ≥ 15 months, as shown during epidemics from the early 1990s.³

In the United States, the recommended age for measles vaccination was 9 months in 1963, 12 months in 1965, 15 months in 1976, and 12 to 15 months since 1998,⁴ whereas Canada opted for administration at 12 months in 1970 and has stayed with that recommendation since.⁵ However, even in settings where nearly all children received 1 dose of vaccine on schedule, measles transmission continued, and additional intervention was needed to achieve control.⁶ Measles vaccine failures were generally thought to be primary (absence of protection immediately after vaccination) rather than secondary (waning of immunity).^{7,8} Based on this hypothesis and the observation that a second dose generally corrected failed seroconverters,^{9–11} many countries implemented 2-dose programs in the 1990s.

Between 1996 and 1997, all Canadian provinces added a second measles dose to their vaccination schedules and conducted mass campaigns to administer a second dose to all school-age children. In Quebec, the second-largest province (population 8 million), 89% of children 5 to 17 years old received a second measles vaccine dose during these campaigns, and the infant schedule was changed to 2 measles–mumps–rubella (MMR) doses at 12 and 18 months of age.¹² After 15 years

of decline, a large measles epidemic occurred in Quebec in 2011, revealing unexpected vulnerability in adolescents previously vaccinated with 2 doses of MMR.^{13,14} An investigation in the high school at the origin of this outbreak reported an overall vaccine effectiveness (VE) of 95.9% with 1 dose and 94.2% with 2 doses.¹⁴ An unexpected finding from this outbreak investigation was that in 2-dose recipients, VE was greater with older age at first dose, from 93% at 12 months to 97.5% at ≥ 15 months.¹⁴ The risk of measles was 2 to 4 times greater when children were first vaccinated between 12 and 14 months versus ≥ 15 months.¹⁴ Older age at the second dose or longer interval between doses did not influence this observation.¹⁴

Although statistically significant, these results were based on a small number (41) of 2-dose cases. It was therefore important to confirm the findings and to determine whether they were generalizable. Furthermore, most adolescents involved in the school outbreak were born to mothers who had previously been measles infected, whereas currently, almost all babies are born to vaccinated mothers who provide lower concentrations of antimeasles antibodies to their babies than mothers who experienced wild virus infection.^{15,16} Because vaccine-induced maternal antibodies are anticipated to disappear at an earlier age, infants born to vaccine-protected mothers may respond better to an earlier dose of measles vaccine than infants from previous birth cohorts born to infected mothers, if indeed interference from maternal antibody is the principal mechanism for the negative effect of age at first pediatric dose on VE.

We therefore conducted a case–control study to estimate the risk of measles by age at first and second dose, adjusting for maternal status (previously infec-

ted versus vaccinated) using all cases in twice-vaccinated school-age patients reported in Quebec in 2011.

METHODS

Measles confirmed by laboratory testing or epidemiologic link is notifiable by both physicians and laboratories in Quebec.¹⁷ Laboratory confirmation requires virus detection by culture or polymerase chain reaction or development of measles-specific immunoglobulin M in absence of recent vaccination. Epidemiologic link requires classic clinical presentation (fever $\geq 38.3^{\circ}\text{C}$ [101°F] and cough or coryza or conjunctivitis and a generalized maculopapular rash for at least 3 days) with epidemiologic link to a laboratory-confirmed measles case.

In this matched case–control study, inclusion criteria for cases and controls were having received 2 doses of measles-containing vaccine, first dose administered at ≥ 12 months of age, second dose administered ≥ 28 days after dose 1 and ≥ 14 days before rash onset in the matched case, and age between 5 and 17 years. Cases included only confirmed measles as defined earlier and reported from across the province to public health between January 1 and December 31, 2011. Controls were matched for the date of birth (± 6 months) and school attended in 2010 to 2011. For each case, 5 controls were randomly selected from the provincial measles vaccination registry among all students meeting matching criteria. The vaccination status and dates of vaccination were ascertained through the provincial vaccination registry and other records. MMR-II (Merck Canada, Montreal, Quebec) was the only MMR vaccine administered to the pediatric cohorts included in this study.

In Canada, people born before 1970 are considered to have been infected by measles.⁵ This year marks the

beginning of the measles vaccination program using live vaccine, and very few patients from the large measles outbreaks in Quebec (1989) or Ontario (1990–1992) were born before that year.^{18,19} Consequently, the status of participants' mothers (infected versus vaccinated) was assigned by year of birth and review of the provincial vaccination registry, which includes all residents born after 1970 regardless of vaccination status. Mothers not found in the registry were considered to have been born before 1970 and categorized as having been infected, and those born in 1970 or later were considered vaccinated.

The odds ratios (ORs) of measles by age at first and second dose and maternal immune status were estimated by multivariable conditional logistic regression.

This work was conducted under legal mandate from the National Director of Public Health, authorized by the Quebec Public Health Act without requirement for research ethics board review.²⁰

RESULTS

In 2011, among the 725 patients with confirmed measles cases,¹³ 507 were between 5 and 17 years of age; 102 had received 2 doses at ≥ 12 months of age, 1 had received 3 doses, 18 had received 1 dose, 337 were unvaccinated, and 49 had unknown vaccination status or no written proof. Of the 102 2-dose cases, 82 were epidemiologically confirmed, and 20 were laboratory confirmed (17 had measles-specific immunoglobulin M, and 3 others had positive viral culture).

The 102 2-dose cases and their 510 matched controls attended 17 schools, with the number of cases per school ranging from 1 to 41 (mean, 6; median, 2). Of the 12 high schools (grades 7–12), 3 accounted for 73% of twice-vaccinated cases; the high school that was first

and most affected (outbreak school) had 41, another had 17, and the third had 16. There were only 6 (6%) cases in 5 elementary schools (range, 1–2 per school). Two-thirds of cases were in boys, who were at significantly higher risk of measles in univariate analysis (OR = 1.97; 95% confidence interval [CI], 1.3–3.1) (Table 1), a pattern also observed among unvaccinated patients (Data not shown, available upon request). Only 11% of cases were 5 to 12 years old at rash onset (2% were < 10 years, 4% were 10–11, 5% were 12). Adolescents 13, 14, 15, and 16 years old contributed disproportionately, with 17%, 20%, 25%, and 20% of all cases, respectively, whereas 17-year-olds represented 8% of the cases. Seventy percent of the mothers of both cases and controls were born before 1970, $\sim 15\%$ between 1970 and 1972 (during which there was still intense measles circulation), and $\sim 14\%$ in 1973 or later. Measles risk did not statistically differ by maternal year of birth (Table 1).

Among participants outside the outbreak school, the first dose of measles vaccine was administered at 12 or 13 months of age in 90% of cases and 72% of controls, whereas 4.8% and 19.6%, respectively, received the first dose at ≥ 15 months (Table 1). With no case first vaccinated at exactly 15 months, we compared 12 months to the broader age category ≥ 15 months, which included few cases. In univariate analysis, the risk of measles was 6.87 (95% CI, 1.59–29.7) and 11.4 (95% CI, 2.5–52.5) times higher when the first dose had been administered at the age of 12 and 13 months, respectively, compared with ≥ 15 months. ORs were lower but still significant in pooled analysis (outbreak school + outside that school). Neither age at second dose nor interval between doses influenced measles risk, regardless of the inclusion or exclusion of participants from the most affected school.

Because the risk of measles in univariate analysis was similar with first dose administered at 12 or 13 months of age, the 2 ages were merged into a single category (12–13 months) in multivariable analyses. In multivariable analyses, only age at first dose and gender remained significantly associated with measles risk (Table 2). The effect of age at first dose was not confounded by gender, age at second dose, interval between doses, or maternal birth year. In participants outside the outbreak school, when the first dose was administered at 12 to 13 versus ≥ 15 months of age, measles risk was 6.2 times higher (95% CI, 1.33–29.3; $P = .02$), and in pooled analysis it was 5.2 times higher (95% CI, 1.91–14.26; $P = .0013$). When the first dose was administered at 14 versus ≥ 15 months of age, the risk was twice as high but did not reach statistical significance. In children who received their first dose at 12 to 13 months, the risk of measles was similar if their second dose was administered at ≥ 48 months versus < 24 months old (participants outside the outbreak school OR = 0.72; 95% CI, 0.21–2.29; $P = .69$; all participants, OR = 0.98; 95% CI, 0.35–2.49; $P = .898$).

The risk of measles in children who had received their first dose at 12 to 13 versus ≥ 15 months stratified by maternal birth year could not be assessed with matching preserved. Because the overall crude risk estimate was similar with matched (conditional logistic regression) and unmatched (unconditional logistic regression) analysis (OR 5.26 vs 5.01) (Table 3), we conducted unmatched stratified exploration. The trend of greater risk with first dose at 12 to 13 versus ≥ 15 months was present both in children whose mothers were born before 1970 and those born later but was more pronounced in the former (OR = 6.23 and 3.22, respectively) (Table 3). Only the OR for participants whose mothers were born before 1970 was statistically significant, but the small

TABLE 1 OR for Measles by Gender, Age, Maternal Birth Year, Age at First and Second Measles Dose, and Interval Between Doses, Estimated by Univariate Conditional Logistic Regression

	Participants Outside the Outbreak School			All Participants		
	Cases (<i>N</i> = 61), <i>n</i> (%)	Controls (<i>N</i> = 305), <i>n</i> (%)	OR (CI 95%)	Cases (<i>N</i> = 102), <i>n</i> (%)	Controls (<i>N</i> = 510), <i>n</i> (%)	OR (CI 95%)
Male gender	41 (67.2)	134 (43.9)	2.60 (1.5–4.7)	68 (66.7)	258 (50.6)	1.97 (1.3–3.1)
Age, y						
5–12	9 (14.8)	48 (15.8)	— ^a	11 (10.8)	64 (12.7)	— ^a
13–14	20 (32.8)	105 (34.4)		37 (36.3)	187 (36.7)	
15–17	32 (52.5)	152 (49.8)		54 (52.9)	259 (50.8)	
Mother's year of birth						
<1970	45 (73.8)	211 (69.2)	Reference	72 (70.6)	356 (69.8)	Reference
1970–1972	9 (14.8)	53 (17.4)	0.79 (0.4–1.7)	16 (15.7)	77 (15.1)	1.02 (0.56–1.86)
1973+	7 (11.5)	41 (13.4)	0.77 (0.3–1.9)	14 (13.7)	77 (15.1)	0.89 (0.47–1.71)
Age at first dose, mo						
12	38 (62.3)	167 (54.8)	6.87 (1.59–29.7)	67 (65.7)	287 (56.3)	4.88 (1.90–12.6)
13	19 (31.2)	53 (17.4)	11.4 (2.47–52.5)	25 (24.5)	80 (15.7)	6.59 (2.39–18.2)
14	2 (3.3)	28 (9.2)	2.20 (0.29–16.5)	5 (4.9)	43 (8.4)	2.47 (0.68–8.96)
15	0	9 (3.0)	Reference ^b	0	18 (3.5)	Reference ^b
16–23	1 (1.6)	28 (9.2)		2 (1.9)	51 (10.0)	
≥24	1 (1.6)	20 (6.6)		3 (2.9)	31 (6.1)	
Age at second dose, no						
<18	2 (3.3)	6 (2.0)	4.23 (0.63–28.4)	4 (3.9)	9 (1.8)	3.92 (0.97–15.5)
18–23	49 (80.3)	212 (69.5)	2.93 (0.97–8.80)	78 (76.5)	352 (69.0)	1.95 (0.91–4.19)
24–47	6 (9.8)	41 (13.4)	1.64 (0.42–6.38)	11 (10.8)	77 (15.1)	1.09 (0.41–2.83)
≥48	4 (6.6)	46 (15.1)	Reference	9 (8.8)	72 (14.1)	Reference
Interval between first and second doses, mo						
<6	15 (24.6)	83 (27.2)	1.29 (0.51–3.24)	24 (23.5)	136 (26.7)	1.13 (0.56–2.29)
6	20 (32.8)	72 (23.6)	2.01 (0.83–4.88)	31 (30.4)	130 (25.5)	1.53 (0.78–3.01)
7–11	16 (26.2)	83 (27.2)	1.36 (0.56–3.27)	29 (28.4)	133 (26.1)	1.39 (0.72–2.70)
12–47	8 (13.1)	43 (14.1)	Reference	12 (11.8)	71 (13.9)	Reference
≥48	2 (3.3)	24 (7.9)		6 (5.9)	40 (7.8)	

^a Not appropriate, matching variable.

^b Reference is all ages ≥15 months.

^c Reference is all interval ≥12 months.

number of participants with younger mothers limits power and precludes definitive conclusions.

DISCUSSION

Outbreak investigation of the high school that triggered the 2011 measles epidemic in Quebec suggested that the risk of measles in 2-dose recipients was significantly higher (2–4 times) when measles vaccine was first administered at 12 versus ≥15 months of age.¹⁵ The current study confirms that this effect was a generalized phenomenon even outside the outbreak school, most evident in twice-vaccinated older versus younger children. Although the effect of age at first dose was most pronounced in children born to moth-

ers who had probably been infected by measles virus, it was also evident in children born to vaccinated mothers but with less certainty.

Across the 26-year period during which Canada relied on a single dose of measles vaccine delivered at 12 months of age (1970–1996), there was strong evidence of greater protection with delivery of this dose at ≥15 months.⁵ The greater vulnerability of those vaccinated at 12 months was reasoned to be caused by interference from maternal antibodies, addressed through second-dose administration.^{9–11,21} Measles vaccine protection thereafter was considered to provide lifelong immunity.⁸ Increasing the age of the first dose to 15 months in a 2-dose program was therefore assumed unnecessary.

Our findings challenge this assumption.

A pooled fivefold greater risk of measles among those whose first MMR dose was administered at 12 to 13 vs ≥15 months is concerning, especially in the context of measles elimination efforts that require high levels of immunity. Previous serologic studies^{7,10,22–26} based on age at first dose are consistent with our epidemiologic observations. Although caution is needed in the interpretation of immunogenicity findings based on laboratory, assay, and protective thresholds applied, serologic studies have shown that early age at first dose leaves an imprint that affects both the immediate second-dose antibody response and persistence. Children first vaccinated at 12 months compared

TABLE 2 OR of Measles Associated With Age at First Measles Vaccine Dose in Multivariate Analysis (Conditional Regression)

Adjusting Covariates	Participants Outside the Outbreak School			All Participants		
	Covariates			Covariates		
	Age at First Dose, mo			Age at First Dose, mo		
	12–13	14	15+	12–13	14	15+
Crude	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Gender (ref female)	7.81 (1.83–33.30)	2.19 (0.29–16.3)	Reference	5.26 (2.06–13.40)	2.44 (0.67–8.84)	Reference
Age at second dose (ref <24 mo)	7.15 (1.66–30.69)	2.01 (0.27–15.1)	Reference	5.1 (2.00–13.03)	2.34 (0.64–8.51)	Reference
	6.71 (1.45–31.1)	1.93 (0.25–15.1)	Reference	5.05 (1.86–13.75)	2.38 (0.63–8.99)	Reference
Mother's year of birth (ref before 1970)	7.71 (1.81–32.8)	2.16 (0.29–16.1)	Reference	5.27 (2.07–13.44)	2.44 (0.67–8.87)	Reference
All above factors	6.24 (1.33–29.3)	1.88 (0.24–14.9)	Reference	5.21 (1.91–14.26)	2.54 (0.67–9.64)	Reference

with ≥ 13 months are less likely to seroconvert after reimmunization and to have significantly lower antibody levels.¹⁰ This phenomenon has also been noted in children vaccinated younger than 12 months.^{7,22,23} Children without detectable plaque reduction neutralization antibody after a first dose responded to revaccination with a primary-type response and maintained antibody titers after revaccination above levels believed to be protective, whereas revaccination of children with low levels of plaque reduction neutralization antibody induced a secondary-type response, with antibodies returning rapidly to levels below protective threshold.²⁴ In Germany, among ~ 7000 2-dose recipients, the proportion without detectable antibodies decreased steadily with older age at first dose to reach a nadir between 18 and 23 months.²⁵ The proportion seronegative also increased with time since the second dose, and the proportion seronegative ≥ 6 years after the second dose was similar to that observed in single-dose recipients.²⁵ Similarly, in the United States, increased antibody titers in response to a second MMR dose rapidly returned to prebooster levels, and most subjects (72%, 13/18) with low titers 10 years after boosting were also in the lowest quartile for antibodies before boost.²⁶ This “return” to the level of protection afforded by the first dose based on time elapsed since the second dose is consistent with the similar VE we observed after 1 or 2 doses (95.9% vs 94.2%, respectively) during our recent school outbreak investigation.¹⁵

The risk associated with an early age at first dose was present but less pronounced in children born to vaccinated mothers than in children born to infected mothers. This evidence is limited by the small number of participants born to vaccinated mothers and the use of the mothers’ birth year (before 1970) as

TABLE 3 OR of Measles Associated With Age at First Measles Vaccine Dose, in Overall Matched and Unmatched Logistic Regression and Stratified by Maternal Year of Birth (Unmatched Logistic Regression, All Participants)

Maternal Year of Birth	Age at First Dose, mo	Cases	Controls	OR (95% CI)
Overall matched logistic regression	12–13	92	367	5.26 (2.06–13.4)
	14	5	43	2.44 (0.67–8.84)
	≥15	5	100	Reference
Overall unmatched logistic regression	12–13	92	367	5.01 (1.99–12.7)
	14	5	43	2.33 (0.60–8.02)
Stratified analysis				
<1970	≥15	5	100	Reference
	12–13	65	254	6.23 (1.90–20.4)
	14	4	29	3.37 (0.71–15.9)
≥1970	≥15	3	73	Reference
	12–13	27	103	3.22 (0.72–14.4)
	14	1	14	0.94 (0.08–11.6)
	≥15	2	27	Reference

a proxy for having been measles infected. Despite good vaccine coverage when the Quebec universal program began in 1970, low-level transmission continued (Supplemental Fig 1) for a few years. As a result, some mothers born since 1970 may have received vaccine but also been infected, leading to misclassification tending to erroneously suggest the same pattern for children born to vaccinated mothers. Because more infants are born to vaccinated mothers now than in the current study, the current phenomenon may be partly historical. However, even in the absence of maternal antibodies, the immune response to vaccination improves with older age at first dose with respect to both titer and avidity.^{27,28} These observations are limited to vaccination between 6 and 12 months of age but suggest that maturation of the immune system probably also plays an important role in the quality and durability of protection.²⁷

The current study has other limitations. It was not possible to estimate absolute VE because that requires the comparison of vaccinated and unvaccinated people, and most with “no dose” in the provincial registry were in fact vaccinated but with missing data. The higher incidence in

adolescents (75.6 per 100 000) compared with adults 18 to 35 years old (5.3 per 100 000) may be explained by the greater and more intense exposure opportunities associated with the school outbreak, which may have overcome whatever protection teenagers had. Adolescents also received their 2 doses of MMR at 12 and 18 months through the routine program, whereas most young adults received a monovalent measles vaccine as their second dose at school age during the 1996 mass campaign. The small number of cases (5) in patients who received their first dose at ≥15 months of age may raise concerns about unstable estimates, although statistical power and precision would be driven by the magnitude of the difference in risk by age at first dose rather than the absolute cell size. However, the small number of cases in patients with first vaccination at ≥15 months precluded additional stratification to define an optimal age for protection. Our results cannot be explained by the nature of the vaccine because all participants received the Merck MMR-II, virtually the only measles-containing product used in North America at that time. Mis-handling or other local factors affecting vaccine quality would not explain

a selective effect with first dose by age but would affect all vaccinated people. Finally, we observed a predominance of boys among cases that we could not explain; the schools affected included a gender mix, and other social context (eg, sports teams) could not explain this gender pattern. Ultimately, however, gender had no confounding effect on the association between measles and age at first dose that we report.

In the United States, despite several measles importations in 2011, none triggered epidemic spread. This may be partly explained by differences in control measures, vaccine coverage, or chance opportunities for super-spreading ignition events. However, 2 other factors may have contributed to the better protection of US adolescents in 2011: older age at first dose and a greater proportion born to vaccinated mothers. In 1989, the Advisory Committee on Immunization Practices and the American Academy of Family Physicians recommended 2 measles doses with the first dose at 15 months.⁴ In 1998, the recommended age for the first dose was changed to 12 to 15 months.²⁹ In 2011, adolescents 13 to 16 years old were born between 1995 and 1998. The US National Immunization Survey shows that the proportion of children aged 19 to 35 months who received their first MMR dose before 13 months increased from 31% in 1997 to 44.7% in 2001,³⁰ still lower than the 56% in our 13- to 16-year-old controls. US adolescents were also more likely to be born to vaccinated mothers. Because the US measles program started in the early 1960s, women ≤30 years old in 1995 to 1998 were mostly vaccinated and gave birth to two-thirds of the babies. In contrast, 70% of our cases and controls were born to mothers presumed to have been infected (born before 1970). Because children in both the United States and Canada are now born to vaccinated mothers, the effect of age at first dose may become

less pronounced. In guiding the optimal timing of primary immunization, it is necessary to weigh our findings against the recognized severity of measles in infants and VE in protecting against that, especially in the context of an outbreak.²¹

Currently, measles has been eliminated from the Americas, and global experience overwhelmingly supports durable immunity from 2 doses of measles vaccine. However, the unexpected vulnerability we have identified in twice-vaccinated people during

the epidemic in Quebec should be considered a signal warranting additional investigation. In particular, other locations with ongoing measles activity can explore the epidemiologic associations we have raised, and serosurveys of infants who received an early versus later first dose of MMR would be informative.

CONCLUSIONS

Although unvaccinated people should remain the prime target for measles

vaccination, the unexpected vulnerability we have identified in twice-vaccinated people could ultimately lead to failed measles elimination efforts. If the effect of early vaccination permanently alters the ability to respond to subsequent doses, even adding a third or fourth dose may not provide long-lasting protection. Therefore, it is critical to understand the mechanisms of primary vaccine failure or loss of vaccine protection that our findings may signal.

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