

# Higher Risk of Measles When the First Dose of a 2-Dose Schedule of Measles Vaccine Is Given at 12–14 Months Versus 15 Months of Age

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(See the Editorial Commentary by Seward and Orenstein, on pages 403–5.)

**Background.** In 2011, >750 cases of measles were reported in Quebec, Canada, where a routine 2-dose measles immunization schedule, in which measles vaccine is given at 12 and 18 months of age, had been in effect since 1996. Effectiveness of this schedule was assessed during a high school outbreak.

**Methods.** Cases were identified by passive followed by active surveillance. Classical cases met the national surveillance definition; attenuated cases showed clinical signs and high measles-specific immunoglobulin G but did not fulfill all classical criteria. Immunization status was ascertained from written records, and vaccine effectiveness (VE) was calculated as  $1 - [(risk\ of\ measles\ in\ vaccinated\ individuals)/(risk\ in\ unvaccinated\ individuals)] \times 100\%$ .

**Results.** Among 1306 students, 110 measles cases were identified; 98 were classical cases, and 12 were attenuated cases. The attack rates among unvaccinated and fully vaccinated students were 82% and 4.8%, respectively. The VE among 2-dose recipients was 95.5% against classical and 94.2% against all (classical + attenuated) measles. Among 2-dose recipients, attack rates with first immunization at 12 and  $\geq 15$  months of age were 5.8% and 2.0%, respectively, with corresponding VE values of 93.0% and 97.5%. The risk of measles in 2-dose recipients was significantly (3–4-fold) higher when vaccine was first administered at 12 months of age, compared with  $\geq 15$  months of age ( $P = .04$ ).

**Conclusions.** Despite compliance with the recommended 2-dose measles immunization schedule, 6% of high school students were susceptible during this outbreak. Residual susceptibility was 2–4-fold higher among 2-dose recipients who had received the first dose of vaccine prior to 15 months of age. If confirmed in other settings, these results suggest that administration of the first dose of measles vaccine before 15 months of age may not be optimal for measles elimination efforts.

Measles elimination goals have been adopted by a number of countries, including Canada. A high level of population immunity (>93%–95% in all districts) is required to prevent sustained transmission [1]. Such

high levels cannot be achieved with a single dose of measles vaccine, which has an estimated effectiveness of approximately 92% (interquartile range, 86%–96%) [2]. Immunogenicity studies suggest that approximately 90% of children who fail to respond to a first dose will seroconvert following a second dose [3–5]. A 2-dose measles immunization schedule has therefore been recommended to achieve elimination goals. In Canada, mass immunization campaigns targeting children aged 1–17 years were conducted in 1996–1997 to provide a second dose of a formulation containing measles vaccine. A routine pediatric 2-dose measles, mumps, and rubella (MMR) vaccination schedule was also introduced

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at that time, with the first dose given at 12 months and the second dose given at either 18 months or 4–6 years of age, depending on provincial preference [6]. Both schedules were anticipated to protect nearly all twice-immunized children.

In Quebec (population 7.9 million), 89% of school-aged children received a second dose of measles vaccine during the 1996 mass immunization campaign. Thereafter, Quebec administered its routine 2-dose schedule at 12 and 18 months of age. Between 2001–2010, 118 measles cases were reported, including an outbreak of 94 cases in 2007 within networks of unvaccinated children [7]. In 2011, importation of measles virus related to the epidemic in France [8] triggered a large outbreak of >750 cases (9.4 cases/100 000 person-years) in Quebec [9]. This epidemic started in a high school in a rural town (approximately 70 000 inhabitants) and spread rapidly within the associated region, which ultimately contributed nearly 70% of all provincial cases. This area was not implicated in the 2007 outbreak. In this high school, among the 77 measles cases initially reported, in 30%, the patient had received 2 doses of a formulation containing measles vaccine. An investigation was conducted within this school to explore reasons for the high number of cases, including the coverage and effectiveness of the 12- and 18-month, 2-dose schedule.

## METHODS

This work was conducted under legal authority conferred by the Quebec Public Health Act; research ethics board review was not required [10]. The study population included all students from the affected school but excluded staff since their vaccination status could not be reliably ascertained.

### Case Identification

Measles is notifiable in Quebec by both physicians and laboratories. However, at the peak of the outbreak, and except in the event of severe illness, patients were told not to seek medical attention, to avoid infecting others. In an effort to detect undiagnosed cases, the school absenteeism registry was used to contact the parents of all students who had missed school related to possible measles. Active surveillance was also conducted in the first week of June 2011, during which all students answered a short questionnaire assessing the concomitant occurrence of fever and rash or other illness for which measles was evoked since 1 April. The parents of all students who responded “yes” or “don’t know” were called by a nurse to collect information on measles-like symptoms and vaccination status.

Cases were classified as “classical” or “attenuated” as defined in Table 1. Classical cases met the national surveillance case definition and were either laboratory confirmed or epidemiologically linked. Cases were distributed across all grades so that an epidemiological link was assumed for all students of the

**Table 1. Definition of Cases and Vaccine Status**

Category	Definition
Case status	
Classical measles	
Laboratory confirmed	Isolation of measles virus from an appropriate clinical specimen OR detection of measles virus RNA OR detection of measles-specific IgM antibody
Epidemiologically linked	Fever (temperature, $\geq 38.3^{\circ}\text{C}$ ) AND generalized maculopapular rash for at least 3 days AND any of the following: cough, coryza, OR conjunctivitis; an epidemiological link was assumed for all students attending the affected school
Attenuated measles	Measles symptoms without meeting full clinical case definition and showing high titers of measles-specific IgG antibody ( $\geq 2500$ mIU/mL)
Vaccine status	
Unvaccinated	Parent reports that child unvaccinated OR parent unsure of child vaccination AND child always lived in area AND vaccination record shows no dose of measles vaccine given
Vaccinated	
1 dose	Record indicates only 1 dose with date of administration (even if parent reported complete vaccination)
$\geq 2$ doses	Record indicates $\geq 2$ doses with dates of administration
No written proof	Parent report that child vaccinated but no record available
Unknown	Parent not reached or unsure of child vaccination status and no record available

Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M.

affected school. Students with rash or measles-compatible symptoms who did not fully meet clinical criteria had sera collected the first week of July (7–9 weeks after symptom onset) for measles-specific immunoglobulin M (IgM) and immunoglobulin G (IgG) testing by enzyme immunoassay (EIA; Enzygnost; Siemens Healthcare Diagnostics, Deerfield, IL). Those who were IgM negative but had IgG levels unlikely to be attributable to childhood immunization ( $\geq 2500$  mIU/mL) were considered secondary vaccine failures and were classified as attenuated cases [11–14].

### Vaccination

The vaccine these students received during childhood was generally MMR II (Merck Canada), which includes the more attenuated measles virus derived from Enders’ attenuated Edmonston strain. The local public health unit is the sole vaccine provider for this town—vaccine status and date of immunization were therefore captured through review of written records. For those with missing information, parents were contacted to review the child’s personal vaccination booklet

and to inquire about other possible vaccine providers. Vaccine status was defined as in Table 1. Although some ( $n = 20$ ) students received a dose of MMR on 10 or 17 May 2011 as part of the outbreak response, these doses were not considered in assigning vaccine status, since immunization typically requires 10–14 days to induce protection in measles-naive subjects and since <4% of cases occurred after 20 May. The school had no exclusion policy for children not fully vaccinated.

### Statistical Analysis

Vaccine effectiveness (VE) was calculated by comparing the attack rate (AR) in vaccinated students with the AR in unvaccinated students, through calculation of the risk ratio (RR), according to the following equation:

$$VE = [1 - RR_{\text{vaccinated/unvaccinated}}] \times 100\%$$

For the primary analysis, individuals without written proof or with unknown immunization status were excluded. For sensitivity analysis, these students were considered unvaccinated. RRs for measles were adjusted for student grade but not age as these variables were highly correlated. Analysis was performed using SAS 9.2 (SAS Institute, Cary, NC).

## RESULTS

### School Outbreak and Study Population

The index case was a 1-dose vaccinated staff member who became ill 9 days after returning from a Caribbean country. As this corresponds to the measles incubation period and in the absence of measles cases reported in that country, public health investigators suspect measles to have most likely been acquired in Canada at the Montreal airport. While a virus was not recovered from this index case, viruses isolated in secondary cases

were of the D4 genotype circulating in Europe. This case became febrile on 2 April 2011 and started coughing on the 4 April but was in contact with several groups of students until 7 April, when a rash appeared. Between 17–23 April, 10 students became ill (Figure 1). Beginning 29 April, the number of measles cases among students increased rapidly, peaking on 3 May, with 19 cases. The rash onset of the last case was 1 June.

In this high school of 1306 students, the median age was 15 years, and 97% were 12–18 years old (birth year range, 1993–1998). Passive surveillance identified 80 classical and 3 attenuated cases (Figure 2). The school absenteeism registry included 35 possible cases reported by parents, of which 11 were classical and 7 were attenuated. Active surveillance identified 205 students whose questionnaire indicated the possibility of measles-like illness. Their parents were called, and an additional 7 classical and 2 attenuated measles cases were found. Of the 110 student cases identified, 98 were therefore classical (23 laboratory confirmed) and 12 were attenuated (Table 2). Attenuated cases were only found in 2-dose recipients, none of whom had been revaccinated as part of outbreak control. All attenuated cases had IgG levels  $\geq 13\,000$  mIU/mL, except for 2 cases (IgG level, 2963 mIU/mL and 3146 mIU/mL), both of whom had rash, cough, and coryza but no fever. Six other twice-vaccinated students with mild symptoms refused to be tested and were not counted as cases.

### VE Findings

The proportions of students who had received 0, 1, 2, 3, or an unconfirmed/unknown number of measles vaccine doses were 4.7%, 6.8%, 85.1%, 0.4%, and 3.0%, respectively (Table 2). The overall AR was 8.4%, with ARs of 82% in unvaccinated students and 3.4% and 4.8% in 1- and 2-dose vaccine recipients, respectively (Table 3). Nearly half of all measles cases (53 of

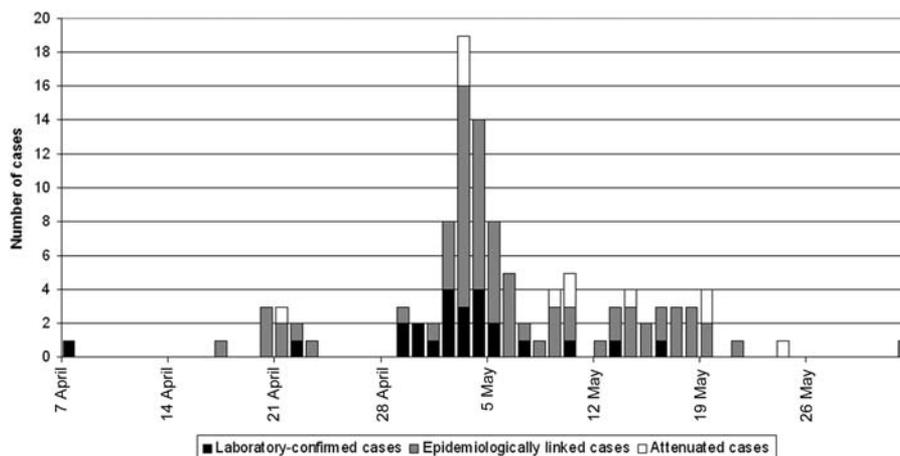
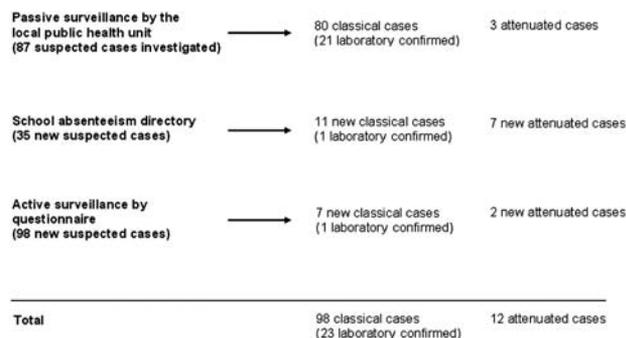


Figure 1. Measles epidemic curve in high school.



**Figure 2.** Measles cases detected by passive surveillance, school absenteeism directory, and active surveillance.

110) occurred in 2-dose recipients, and of these, 23% (12 of 53) were attenuated. Only MMR II had been administered to these cases, except for 2, whose second dose was a monovalent measles vaccine (Connaught, Canada) received during the 1996 mass campaign.

One-dose VE against classical measles was 95.9% (95% confidence interval [CI], 87.4%–98.7%). Two-dose VE was 95.5% (95% CI, 93.8%–96.7%) against classical measles and 94.2% (95% CI, 92.9%–95.6%) against all (classical plus attenuated) measles (Table 3). Adjustment for school grade (grade 7–9 vs other grades) changed the VE estimates only minimally (by approximately 0.3%). In sensitivity analysis, assuming that students with unconfirmed or unknown vaccine status were unvaccinated, VE against classical measles and all (classical plus attenuated) measles in 2-dose recipients was 93.1% (95% CI, 90.2%–95.1%) and 91.1% (95% CI, 87.7%–93.5%), respectively. When analyzed by year of age, there was no decrease in VE between 12 and 17 years of age (12 years, 77%; 13 years, 94%; 14 years, 95%; 15 years, 92%; 16 years, 95%; and 17 years, 87%).

### Influence of Age at First Vaccine Dose

Of the 1116 students who had received  $\geq 2$  doses of measles vaccine, 660 (59.2%), 230 (20.6%), and 198 (17.9%) received their first dose at 12 months, 13–14 months, and  $\geq 15$  months

**Table 2. Characteristics of Students, by Grade**

Characteristic	Grade 7	Grade 8	Grade 9	Grade 10	Grade 11	SE Groups	Total
Students, no. (row %)	253 (19)	283 (22)	260 (20)	218 (17)	172 (13)	120 (9)	1306 (100)
Sex							
Female	91 (35.9)	117 (41.3)	101 (38.9)	98 (45)	90 (52.3)	44 (36.7)	541 (41.4)
Male	162 (64)	166 (58.7)	159 (61.1)	120 (55)	82 (47.7)	76 (63.3)	765 (58.6)
Age, years							
12	107 (42.3)	1 (0.4)	0	0	0	2 (1.7)	110 (8.4)
13	133 (52.6)	131 (46.3)	0	0	0	15 (12.5)	279 (21.4)
14	13 (5.1)	132 (46.6)	105 (40.4)	1 (0.5)	0	17 (14.2)	268 (20.5)
15	0	17 (6.0)	136 (52.3)	107 (49.1)	0	15 (12.5)	275 (21.1)
16	0	2 (0.7)	19 (7.3)	102 (46.8)	83 (48.3)	19 (15.8)	225 (17.2)
17	0	0	0	8 (3.7)	84 (48.8)	17 (14.2)	109 (8.4)
$\geq 18$	0	0	0	0	5 (2.9)	35 (29.2)	40 (3.1)
Median (range)	...	...	...	...	...	...	14.9 (12.5–21.5)
Vaccination status							
0 dose	14 (5.5)	15 (5.3)	15 (5.8)	7 (3.2)	4 (2.3)	6 (5.0)	61 (4.7)
1 dose	18 (7.1)	17 (6.0)	17 (6.5)	12 (5.5)	11 (6.4)	14 (11.7)	89 (6.8)
2 doses	210 (83.0)	243 (85.9)	224 (86.2)	190 (87.7)	151 (87.8)	93 (77.5)	1111 (85.1)
3 doses	0	1 (0.4)	1 (0.4)	3 (1.4)	0	0	5 (0.4)
Vaccinated, no written proof	9 (3.6)	4 (1.4)	2 (0.8)	3 (1.4)	4 (2.3)	6 (5.0)	28 (2.1)
Unknown	2 (0.8)	3 (1.1)	1 (0.4)	3 (1.4)	2 (1.2)	1 (0.8)	12 (0.9)
Measles cases							
Classical							
Laboratory confirmed	5	7	8	3	0	0	23 (20.9)
Epidemiologically linked	18	17	19	10	8	3	75 (68.2)
Attenuated	2	2	5	1	2	0	12 (10.9)
Total no. (AR, %)	25 (9.9)	26 (9.2)	32 (12.3)	14 (6.4)	10 (5.8)	3 (2.5)	110 (8.4)

Data are no. or no. (column %) of students, unless otherwise indicated.

Abbreviations: AR, attack rate; SE, special education.

**Table 3. Attack Rate of Measles, by Vaccination Status, and Vaccine Effectiveness, by Number of Doses**

Variable	Vaccination Status					Total
	0 Dose	1 Dose	≥2 Doses	Vaccinated No Written Proof	Unknown	
<b>Measles cases</b>						
Classical, no. (AR, %)	50 (82.0)	3 (3.4)	41 (3.7)	2 (7.1)	2 (16.7)	98 (7.5)
Attenuated, no. (AR, %)	0	0	12 (1.1)	0	0	12 (0.9)
Noncases, no.	11	86	1063	26	10	1196
Total no.	61	89	1116	28	12	1306
<b>Vaccine effectiveness, % (95% CI)</b>						
Classical measles only	...	95.9 (87.4–98.7)	95.5 (93.8–96.7)	...	...	...
All measles	...	95.9 (87.4–98.7)	94.2 (92.9–95.6)	...	...	...

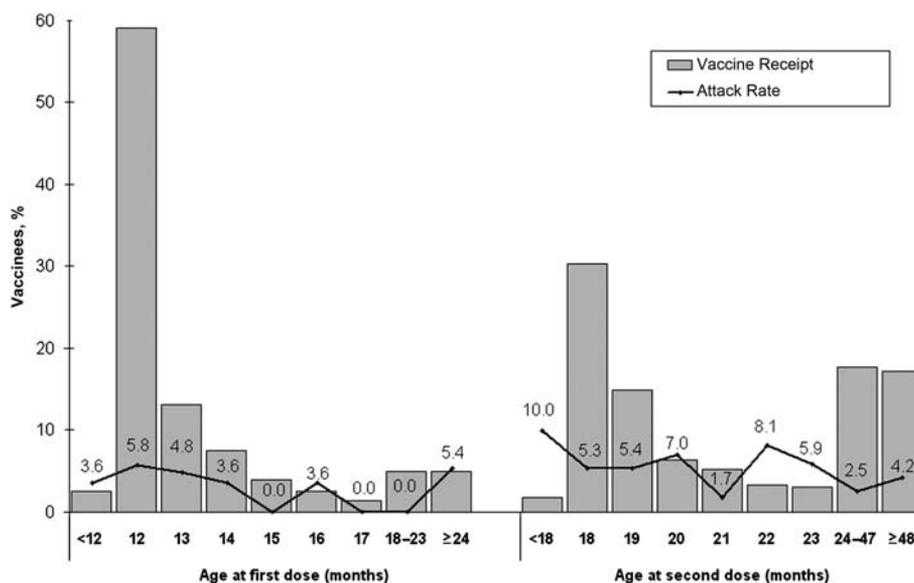
Abbreviations: AR, attack rate; CI, confidence interval.

of age, respectively (Figure 3). The corresponding measles AR was 5.8% (38 of 660), 4.3% (10 of 230), and 2.0% (4 of 198), respectively, and the VE was 93.0%, 94.7%, and 97.5%, respectively (Table 4). In students who received both doses between 12 and 23 months of age, the AR was 5.6% (40 of 708), and the VE was 93.1% (95% CI, 90.5%–95.0%). Among students who received their first dose at ≥12 months of age and their second dose at ≥48 months of age, the AR was 3.7% (7 of 188), and the VE was 95% (95% CI, 90.5%–97.8%).

In students who received their first dose at 12 months of age, the AR was higher with a second dose administered exactly 6 months later, compared with an interval ≥12 months (5.4% vs 3.8%;  $P = .47$ ), but the reverse trend was observed in those who received their first dose at ≥13 months of

age (Figure 4). Overall, a longer interval to the second dose was not more protective.

Compared with students receiving their first measles vaccine dose at ≥15 months, the RRs for classical measles in those first vaccinated at 12 or 13–14 months of age were 4.35 (95% CI, 1.05–18.1;  $P = .04$ ) and 3.87 (95% CI, .85–17.7;  $P = .08$ ), respectively, and for all (classical plus attenuated) measles were 2.85 (95% CI, 1.03–7.9;  $P = .04$ ) and 2.15 (95% CI, .69–6.76;  $P = .19$ ), respectively (Table 4). The RR of measles comparing 2 doses given between 12 and 23 months of age to a first dose given at ≥12 months of age and the second at ≥48 months of age was not significantly higher for classical cases (RR, 1.59; 95% CI, .63–4.05;  $P = .33$ ) or all cases (RR, 1.52; 95% CI, .69–3.33;  $P = .30$ ).



**Figure 3.** Distribution of the age at first and second measles virus dose and attack rate among 2-dose recipients.

**Table 4. Vaccine Effectiveness and Risk Ratio of Measles, by Age at First Dose**

Variable	12 Months	13–14 Months	≥15 Months
Cases, no.			
Classical	29	9	2
Attenuated	9	1	2
Total	38	10	4
Noncases, no.			
	622	220	194
Vaccine effectiveness, % (95% CI)			
Classical measles only	94.6 (92.2–96.3)	95.2 (90.8–97.5)	98.8 (95.1–99.7)
All measles	93.0 (90.2–95.0)	94.7 (90.2–97.1)	97.5 (93.5–99.1)
RR (95% CI)			
Classical measles only	4.35 (1.05–18.07)	3.87 (0.85–17.72)	Reference
All measles	2.85 (1.03–7.89)	2.15 (0.69–6.76)	Reference

Data do not include the 28 students (1 case) whose first dose was administered before 12 months of age.

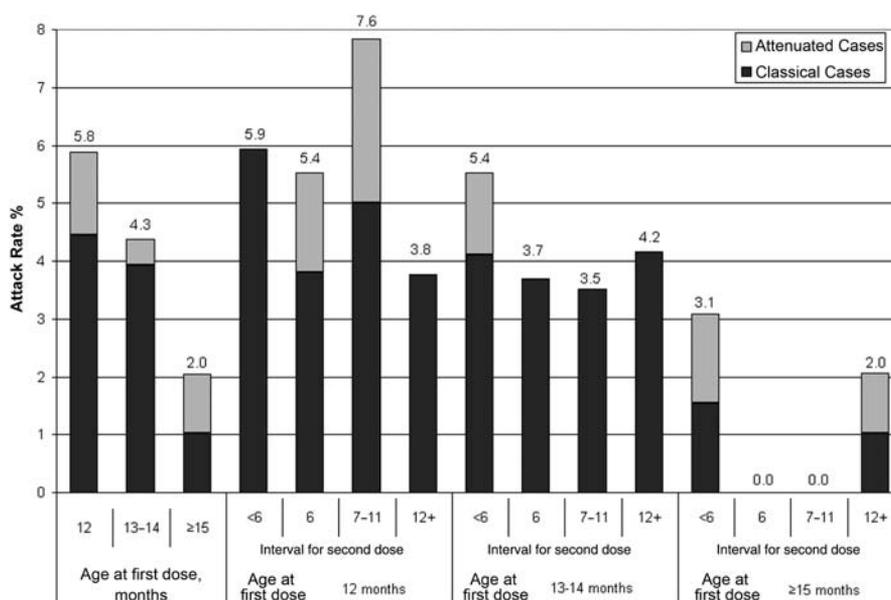
Abbreviation: CI, confidence interval.

## DISCUSSION

Our investigation of this school with several generations of sustained measles transmission revealed a higher than expected AR (4.8%) and proportion of cases (47%) among fully immunized 2-dose recipients and a low VE of 94%. It also showed a significant association between measles risk and the age at which the first dose was administered. Those reporting perfect compliance with the recommended 2-dose schedule beginning at 12 months of age had a risk of measles that was

significantly (3–4-fold) higher than that for students whose first dose had been delayed to at least 15 months.

Given that 5% of the student population at this high school was unimmunized and that 7% had received only 1 dose, sustained transmission following initial importation is not itself surprising. While 1- and 2-dose recipients had a similar VE, relatively few had received 1 dose, and the large CIs prevent any firm conclusions to be drawn. Airborne transmission and a high reproductive number are hallmarks of measles and explain the emphasis on high immunization coverage as an



**Figure 4.** Attack rate of measles according to age at first dose and interval (in months) between first and second dose.

important public health goal [15, 16]. The school that was the focus of this study was far more affected than other schools in the region. However, vaccine coverage at this school differed only slightly (1%–2%) as compared to elsewhere in the province, where surveys have shown that 96% and 85% of children have received at least 1 or 2 measles vaccine doses, respectively, by 2 years of age [17, 18]. It is unlikely that the proportion of susceptible students among 2-dose recipients was different in this school as compared to other schools. Student characteristics per se are unlikely to explain the high AR, but specific circumstances, including socioenvironmental factors, may have facilitated the initial superspreading event, infecting the first group of 10 secondary cases and triggering the subsequent cascade of infections that affected 82% of unvaccinated students. This outbreak differed importantly from the minimal number of secondary cases directly infected by each of the few hundred measles cases imported to Canada or the United States in the past decade. Models have shown that, under the elimination threshold, measles has difficulty penetrating the population, with marked heterogeneity in transmission (some superspreaders and many low transmitters) that may cause epidemics if initial circumstances are favorable [19].

The intensity of exposure opportunities in this school provided a good test of the effectiveness of the recommended 2-dose immunization schedule. Among the 2-dose recipients with vaccine failure, nearly 25% did not exhibit classic measles features. Milder symptoms in vaccinated cases have often been reported [11–14]. Our overall 94.2% VE with its tight CI (92.9%–95.6%) is the most robust result of this study. It is similar to VEs reported in a recent review comparing 2-dose recipients to unvaccinated individuals (median VE, 94.1%; 95% CI, 88.3%–98.3%) [2]. The VE per age at first dose in our outbreak showed incremental protection from ages 12 months to 13–14 months and  $\geq 15$  months, but the CIs of these estimates were overlapping. VE is calculated by comparing the AR between vaccinated and unvaccinated individuals. When ARs were instead compared by age at first dose only in 2-dose recipients, the risk decreased from 5.75% among those aged 12 months, to 4.35% and 2% among those aged 13–14 and  $\geq 15$  months, respectively, with a significant difference between ARs at  $\geq 15$  months versus 12 months of age. This age-related comparison is as valid an approach as estimating VE and suggests a real and significant negative effect of earlier age at first immunization. ARs did not decrease with longer interval between the first and second doses (Figure 4), suggesting that the negative impact of an early first dose is not overcome by a second dose in a substantial proportion of children. This age-at-first-dose effect among 2-dose recipients has been reported previously in Canada in a case-control study conducted between 1990 and 1996 [20]. As in the current study,

protection was not influenced by the subsequent interval between the first and second doses.

This study has several strengths, such as the large sample size, intense measles exposure, active search for cases, and availability of written immunization records in most cases. In this region, there had been almost no measles cases in the previous 20 years; therefore, previous measles infection cannot have skewed our results. When these students received their first MMR II dose, no other vaccines were administered concomitantly, excluding the possibility of interference. There are, however, several limitations. Some cases may have been missed. If there were cases among the 6 vaccinated students with attenuated symptoms who refused serological analysis, our VE would be overestimated. A small proportion of the students (3%) had no written proof or unknown immunization status. If these students were mostly unvaccinated, they would also have contributed to the overestimation of VE, although this was explored in sensitivity analysis that showed minimal reduction in VE on that basis. We cannot rule out mishandling of vaccine that could theoretically have contributed to enhanced vulnerability in these students. However, this is unlikely to have gone unnoticed across the multiple birth cohorts included and would not explain the age-related effects of first-dose timing. Although VE may be underestimated when derived within intensely affected settings, this is also unlikely to bias the age-related effects we observed. The risk of measles was not significantly higher in students who received both doses between ages 12 and 23 months, compared with those whose second dose was given at  $\geq 48$  months of age (RR, 1.5;  $P = .30$ ). The VE with the second dose at  $\geq 48$  months of age was 95% (95% CI, 90.5%–97.8%), which did not show greater protection. However, because only 188 students received measles vaccine on the basis of the latter schedule, the statistical power was limited, and caution should be used in extrapolating our results to jurisdictions where the second dose is given at 4–6 years. However, in the Ukraine, where 2 doses were administered at 12–15 months and 6 years of age, the overall VE during a large epidemic was also 92%–94%, comparable to our own [21].

Maternal antibodies interfere with the measles vaccine, and titers are typically lower in children born to vaccinated as compared to previously infected mothers [22, 23]. In our study, we did not collect maternal age or maternal immunization/infection history, but many of these mothers were likely to have encountered wild virus. Most were born between 1960 and 1985, and substantial transmission occurred in the 1960s, early 1970s, and even 1989, despite a universal measles vaccination program in Quebec starting in 1970 [24]. If high levels of maternal antibodies explain our results regarding the age at first dose, then this finding may not apply to children born more recently to mothers exposed only to vaccine-strain virus.

However, previous studies have shown that the immune response to the first dose improves with older age at vaccination, even in the absence of maternal antibodies, suggesting that other mechanisms are involved in the suboptimal response to early vaccination [25–28].

The 2-dose strategy recommended at 12 and 18 months of age was based on 4 key assumptions: (1) the young are at high risk of severe complications of measles, (2) residual vulnerability following a first dose of measles vaccine is due to primary failure mostly caused by interference from maternal antibody, (3) nearly everyone with primary failure receiving a second dose will seroconvert and be protected, and (4) vaccine-induced immunity is long lasting [29]. On that basis, the earliest possible administration of a 2-dose schedule beginning at 12 months of age was considered the best programmatic option.

To eliminate measles, overall population susceptibility must be kept below 5% and ideally even lower within confined settings such as schools. If the current schedule leaves a residual 6% susceptibility to measles in fully compliant, 2-dose recipients, regardless of the mechanism, this could seriously impede progress toward elimination. We are unable to resolve whether this susceptibility was caused by primary absence of protection, by secondary waning of immunity over time, or by both factors. The appropriate public health intervention to improve protection will depend upon the immunologic mechanism(s) involved. While our data suggest that administering the first dose of measles vaccine after 15 months of age may significantly reduce overall risk, confirmation of these findings in other settings is required before changes to immunization policy can be considered. In light of recent outbreaks, however, some countries have moved in precisely the opposite direction by placing even greater emphasis on administration of the first-dose of vaccine at 12 or even 9 months of age [30]. Our findings suggest this approach may be counterproductive and that further reflection is warranted. In the meantime, efforts to immunize children who have not received any measles vaccine doses should continue to have the foremost priority since these individuals remain at greatest personal risk and continue to pose the greatest public health threat.

## Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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