A measles outbreak occurred among a highly vaccinated population in Alaska during 1998, providing an opportunity to determine the incremental efficacy of ≥2 doses of measles-containing vaccine (MCV) compared with 1 dose. Of 33 confirmed case patients identified, 31 had been vaccinated with 1 dose of MCV, 1 had received 2 doses, and vaccination status was unknown in 1 case. Seventy percent of cases were school-associated; 58% of cases occurred in 2 high schools. Of 3679 students attending the 2 schools, 50.4% and 45.5% had received ≥2 doses of MCV before measles introduction at the schools. The relative risk of developing measles among persons vaccinated with ≥2 doses of MCV compared with 1 dose was 0.06 (95% confidence interval, 0.01–0.44; \( P < .001 \)), yielding an estimated incremental vaccine efficacy of 94.1% (95% confidence interval, 55.9%–99.2%; \( P < .001 \)). Rapid implementation of a mandatory second-dose MCV requirement probably limited the extent of this outbreak.

In August–November 1998, the largest outbreak of measles in the United States since 1996 occurred in Anchorage, Alaska [1]. Most cases were associated with 2 high schools. A state law requiring 2 doses of measles-containing vaccine (MCV) for all students entering kindergarten or first grade had been in effect since September 1996; therefore, 2-dose coverage was high among Alaska students in kindergarten through grade 3 but unknown among students in grades 4–12. Outbreaks among highly vaccinated populations have been reported elsewhere [2, 3]; however, relatively few data are available to estimate the incremental effectiveness of 2 doses of MCV compared with 1 dose. This outbreak provided a unique opportunity for such an estimate.

**METHODS**

Outbreak epidemiology and response. On 11 August 1998, an unvaccinated 4-year-old child from Japan (index case) had onset of a febrile rash illness while visiting Anchorage, a city of 255,000 persons representing ~40% of Alaska’s population (figure 1). The child and his family arrived in Anchorage from Japan on 29 July. The child was hospitalized for 1 day, and measles was diagnosed by positive result of anti-rubeola IgM capture ELISA. Culture of virus was not undertaken.

No cases were reported during the subsequent 3 weeks, when secondary cases would have been expected. However, on 5 September, 26 days after the onset of rash in the index case patient, an Anchorage high school student aged 16 years developed measles, confirmed by anti-rubeola IgM testing. Subsequently, measles developed in 15 other students and 1 teacher at the same high school (high school A) between 14 September and 4 October. Sixteen additional cases occurred in 5 other Anchorage schools and in the general community. Transmission was documented in 1 of these schools (high school B) but involved only 2 cases.

During the outbreak, possible case patients and their
contacts were identified and investigated according to standard recommendations [4]. A total of 141 possible cases of measles were reported; 33 cases were confirmed. The 33 case patients ranged in age from 2 to 37 years (median, 16 years). Twenty-two patients (67%) were aged 14–17 years. Forty-eight percent of case patients were female. Overall, 31 of the case patients had received 1 dose of MCV, 1 had received 2 doses, and vaccination status was unknown in 1 case. Of the cases, 23 (70%) were school-associated; all of these patients had received ≥1 dose of MCV. There were no serious complications or deaths.

In addition to individual case investigations, the major outbreak control strategy consisted of an emergency order issued by the Alaska Department of Health and Social Services on 25 September. The order required all Anchorage children attending public or private schools and enrolled in kindergarten through grade 12 to have 2 doses of MCV by 16 November 1998 (figure 1).

About 33,000 public school children enrolled in grades 4–12 in the Anchorage school district were affected by the 25 September order that required 2 doses of MCV. By the 16 November compliance date, 98% had provided documentation of 2 doses of MCV to their schools; 345 students (1%) were excluded for lack of documentation, and 322 students (1%) provided medical or religious exemptions. No data were available for students attending private schools. As the proportion of high school A students with 2 doses of MCV increased, transmission within the school ended (figure 2).

Nine of 11 virus isolates were sent to the Centers for Disease Control and Prevention for genotyping [5–7]. All had identical sequences and were classified as genotype D5 [7]. This strain was almost identical to wild measles virus strains circulating in Japan during 1995–1998 [8] (Centers for Disease Control and Prevention, unpublished data, 1999) and was of a different genotype from that of the strain isolated from the Juneau outbreak during 1996, the most recent isolate available from Alaska [9, 10]. The sequence identity between all of the Alaska outbreak isolates was consistent with a single source of infection.

Human experimentation guidelines of the US Department of Health and Human Services were followed during the investigation and control of this outbreak.

Cohort study—incremental vaccine efficacy. A retrospective cohort investigation was conducted at 2 Anchorage high schools in which measles transmission occurred among students. A list of students enrolled at each school during the outbreak was obtained from the Anchorage School District. Medically verified immunization histories maintained on student health records, as documented by school personnel, were used to obtain dates of MCV administration for each student. In addition, information on the physical plant characteristics of both schools was collected.

We calculated the relative risk of developing measles for high school students vaccinated with ≥2 doses of MCV before the outbreak compared with those vaccinated with only 1 dose of MCV. Incremental vaccine efficacy of 2 doses of MCV compared with 1 dose was estimated by using the following equation [11, 12]: incremental vaccine efficacy = (1 − relative risk) × 100%.

Students who had never received MCV were excluded from this calculation. To be classified as having 2 doses of MCV, students must have received ≥2 doses of MCV, separated by ≥28 days, at or after 12 months of age, administered at least 14 days before measles was introduced into their school. Population characteristics were compared for the 2 high school student populations by means of the Kruskal-Wallis H test and the χ² test [13]. Vaccination data from both schools were combined for the incremental efficacy calculation.

Figure 1. Number of confirmed measles cases, by date of rash onset—Anchorage, Alaska, August–November 1998. A confirmed case was laboratory confirmed or met the clinical case definition and was epidemiologically linked to a confirmed case. A clinical case was defined as generalized rash lasting for ≥3 days; temperature ≥38.3°C; and cough, coryza, or conjunctivitis. MCV, measles-containing vaccine.

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RESULTS

The median ages of students at high schools A and B were 17 years (ranges, 13–19 years and 13–21 years, respectively). About 50% of students at each school were male. No common classes were identified for any of the students or the teacher who developed measles. An epidemiological link was established between 1 case at high school A and the first case at high school B; both students had competed in a sporting event between the 2 schools, held 4 days before onset of rash of the high school A student.

At high schools A and B, 50.4% and 45.5%, respectively, of the students had received 2 doses of MCV before introduction of measles into the school (table 1). One high school A student and 7 high school B students had never been vaccinated against measles; these students were excluded from the incremental vaccine efficacy calculation. Among students attending high school A or B who had only 1 dose of MCV, there was no association between development of measles and either age at vaccination (table 2) or years since vaccination (table 3). Having received at least 2 doses of MCV before the outbreak was highly protective; the relative risk of developing measles among persons vaccinated with ≥2 doses of MCV compared with 1 dose was 0.06 (95% confidence interval [CI], 0.01–0.44; P < .001). The estimated incremental efficacy of 2 doses of MCV compared with 1 dose was 94.1% (95% CI, 55.9%–99.2%; P < .001) (table 1).

Physical plant characteristics varied considerably between high schools A and B. High school A’s ventilation system consisted of 12 independent heating/cooling zones that supplied the 305,638 square-foot building with 5–6 cubic feet of air per minute per building occupant by using a minimum of 10% outside air. During the outbreak, 2192 students were enrolled; mean student density was 28 students per classroom.

In comparison, high school B was a 327,885 square-foot building with 27 independent heating/cooling zones. The ventilation system was designed to provide 15 cubic feet of air per minute per person by using a minimum of 10% outside air. In addition, carbon dioxide levels in large gathering areas were actively monitored, and fresh air intake was adjusted to maintain the levels below 800 ppm. During the outbreak, 1487 students were enrolled; mean student density was 27 students per classroom.

DISCUSSION

In 2 schools where nearly 100% of students had received 1 dose of MCV and ~50% had received 2 doses, an outbreak of measles provided a unique opportunity to assess the incremental efficacy of 2 doses of MCV compared with 1 dose. Having received 2 doses of MCV before the outbreak was highly pro-

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**Table 1. Vaccination status and incremental vaccine efficacy of 2 doses of measles-containing vaccine (MCV) compared with 1 dose among students attending high school A or B—Anchorage, Alaska, 1998 (n = 3679).**

<table>
<thead>
<tr>
<th>School</th>
<th>Enrollment</th>
<th>0</th>
<th>1</th>
<th>≥2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2192</td>
<td>0/1</td>
<td>16/1070</td>
<td>0/1105</td>
</tr>
<tr>
<td>B</td>
<td>1487</td>
<td>0/7</td>
<td>1/802</td>
<td>1/676</td>
</tr>
<tr>
<td>Total</td>
<td>3679</td>
<td>0/8</td>
<td>17/1872</td>
<td>1/1781</td>
</tr>
</tbody>
</table>

* Data are no. of students with measles/no. of students without measles. Relative risk of measles in persons with ≥2 doses of MCV compared with 1 dose = 0.06 (95% confidence interval, 0.01–0.44). Incremental vaccine efficacy = (1−relative risk) × 100% = 94% (95% confidence interval, 55.9–99.2%).

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Figure 2. Number of confirmed cases among students attending high school A, by date of rash onset, compared with the proportion of students vaccinated with 2 doses of measles-containing vaccine (MCV)—Anchorage, Alaska, August–November 1998.
Recurrent outbreaks of measles among highly vaccinated school-aged populations in the United States during the late 1980s prompted recommendations that schoolchildren receive 2 doses of MCV, preferably as the combination measles-mumps-rubella vaccine, by the year 2001 [14, 15].

Previous studies of measles outbreaks among highly vaccinated populations have demonstrated the benefits of second-dose requirements [2, 3]. In a report of a measles outbreak at a high school, students vaccinated \( \geq 10 \) years before exposure, independent of age at first vaccination, were at higher risk for developing measles [16]. That outbreak occurred during 1987, and students vaccinated \( \geq 10 \) years previously were vaccinated before 1980. Several studies have documented an increased risk of vaccine failure among persons receiving MCV before 1980 compared with those vaccinated later; however, evidence to the contrary also exists [3, 17]. A recent investigation of a measles outbreak among secondary school students found no association between vaccine failure and years since vaccination; however, vaccine failure was significantly more likely to occur among persons vaccinated at age 12–14 months compared with those vaccinated at \( \geq 15 \) months of age [3]. Among students in this investigation, the risk of measles virus infection did not increase with increasing time since vaccination and was not associated with age at vaccination. In addition, only 194 of 1889 students with 1 dose of MCV had received their vaccination at \( <15 \) months; of these, only 1 student developed measles, possibly limiting our ability to detect any difference in risk associated with age at vaccination.

Traditional vaccine-efficacy calculations determine the relative risk of developing disease among vaccinated persons compared with unvaccinated persons. The incremental vaccine efficacy calculated here compared persons vaccinated with \( \geq 2 \) doses of MCV with persons vaccinated with only 1 dose. Obtaining accurate estimates of vaccine efficacy requires that persons included in the calculation, both between and among comparison groups, be comparable except for vaccination status. Useful criteria for comparability include a uniform case definition, equal ascertainment of cases, verification of vaccination status, and determination that equal exposure to disease occurred \([11, 12]\). Although the student populations at both high schools met the first 3 criteria, equality of exposure was more difficult to quantify. Variations in exposure may have occurred because of environmental and host factors. Differences existed between the physical environments, particularly the ventilation systems, at high schools A and B; however, it is difficult to know how to apply these environmental data. No cases of measles were identified among students sharing classrooms with case patients at either school. The student populations at both schools were very similar in age and sex distribution and the proportion of students previously vaccinated with 2 doses of MCV. Also, individual calculations for incremental vaccine efficacy at each high school had similar point estimates and overlapping 95% CIs. On the other hand, the occurrence of 16 cases at high school A compared with only 2 cases at high school B would argue that some differences in exposure existed. However, if exposure at high school B was less than at high school A, the effect on incremental vaccine efficacy calculations would seemingly be small.

The genotyping of virus isolates contributed to our understanding of the source of this outbreak and is an important component of US measles elimination activities. Although virus was not cultured from the index case, genotyping of available isolates from the outbreak provided evidence consistent with the background of the index case that the outbreak was caused by importation from Japan and a single source of infection.

Substantial progress was made toward meeting the 2001 goal for all US schoolchildren to have 2 doses of MCV. As of the fall of 2001, all but 1 state (Idaho) had implemented second-dose requirements, providing coverage for 82% of all US schoolchildren [18]. Although the costs associated with implementing

### Table 2. Attack rates, by age at vaccination with measles-containing vaccine (MCV), for students attending high school A or B vaccinated with only 1 dose of MCV before the outbreak—Anchorage, Alaska, 1998 \( (n = 1889) \).

<table>
<thead>
<tr>
<th>Age (months) at vaccination</th>
<th>No. of cases</th>
<th>Total students</th>
<th>Attack rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt;12)</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>12–13</td>
<td>0</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>156</td>
<td>0.6</td>
</tr>
<tr>
<td>15</td>
<td>7</td>
<td>519</td>
<td>1.3</td>
</tr>
<tr>
<td>(&gt;15)</td>
<td>10</td>
<td>1176</td>
<td>0.9</td>
</tr>
</tbody>
</table>

**NOTE.** Mantel-Haenszel \( \chi^2 = 1.5, P = .82 \).
second-dose requirements are large, these costs should be weighed against those associated with outbreak response, which can quickly consume available resources and may deplete funds available for other public health functions. Others have debated the merits of implementing a mandatory second-dose MCV policy as an outbreak control measure; however, there is general agreement that a universal 2-dose MCV policy for schoolchildren would have prevented outbreaks [3, 9, 17]. The occurrence of measles transmission at 2 Anchorage high schools despite nearly half of the students having had 2 doses of MCV suggests that nearly complete coverage with 2 doses of MCV may be required to prevent cases. The rapid implementation of a mandatory second-dose MCV requirement probably limited the extent of this outbreak and will help prevent future outbreaks in Alaska schools. Although available laboratory and epidemiological evidence suggest that endemic measles transmission in the United States has been interrupted, outbreaks may continue to occur when imported measles virus is introduced into an incompletely vaccinated population [1, 5, 19].

References