Impact of a Third Dose of Measles-Mumps-Rubella Vaccine on a Mumps Outbreak

WHAT’S KNOWN ON THIS SUBJECT: Mumps outbreaks continue to occur among unvaccinated and highly vaccinated populations. In highly vaccinated populations, options for outbreak control are limited. No previous study has documented the impact of a third measles-mumps-rubella (MMR) vaccine dose on a mumps outbreak.

WHAT THIS STUDY ADDS: Our study assessed the use of a third MMR vaccine dose for mumps outbreak control in a setting with preexisting high 2-dose vaccine coverage. The findings suggest a potential role of MMR vaccine for outbreak control in such limited settings.

abstract

BACKGROUND AND OBJECTIVE: During 2009–2010, a northeastern US religious community experienced a large mumps outbreak despite high 2-dose measles-mumps-rubella (MMR) vaccine coverage. A third dose of MMR vaccine was offered to students in an affected community in an effort to control the outbreak.

METHODS: Eligible sixth- to 12th-grade students in 3 schools were offered a third dose of MMR vaccine. Baseline and follow-up surveys and physician case reports were used to monitor mumps attack rates (ARs). We calculated ARs for defined 3-week periods before and after the intervention.

RESULTS: Of 2265 eligible students, 2178 (96.2%) provided documentation of having received 2 previous doses of MMR vaccine, and a high proportion (1755 or 80.6%) chose to receive an additional vaccine dose. The overall AR for all sixth- to 12th-grade students declined from 4.93% in the prevaccination period to 0.13% after vaccination ($P < .001$). Villagewide, overall AR declined by 75.6% after the intervention. A decline occurred in all age groups but was significantly greater (96.0%) among 11- to 17-year-olds, the age group targeted for vaccination, than among all other age groups. The proportions of adverse events reported were lower than or within the range of those in previous reports of first- and second-dose MMR vaccine studies.

CONCLUSIONS: This is the first study to assess the impact of a third MMR vaccine dose for mumps outbreak control. The decline in incidence shortly after the intervention suggests that a third dose of MMR vaccine may help control mumps outbreaks among populations with preexisting high 2-dose vaccine coverage. Pediatrics 2012;130:1–8
Before the introduction of mumps vaccine, epidemics of mumps occurred throughout the United States, frequently in crowded settings such as prisons, orphanages, schools, and military facilities.1 In 1967, a live mumps virus vaccine was licensed in the United States. In 1977, the Advisory Committee on Immunization Practices (ACIP) recommended 1 dose of mumps vaccine for all children aged 12 months or older.2 After this, mumps incidence declined rapidly from 50 to 251 reported cases/100 000 persons before 1967 to 2/100 000 persons in 1988.3 In 1989, to enhance measles control, ACIP recommended a second dose of measles-mumps-rubella (MMR) vaccine; widespread use of 2 doses of MMR vaccine resulted in further declines in mumps incidence.4 During 2000–2005, historic annual lows of <300 mumps cases were reported (incidence 0.1/100 000 persons). Coverage with at least 1 dose of MMR vaccine was between 90.5% and 91.5% nationwide among children aged 19 to 35 months.5,6 In 2006, according to the National Immunization Survey, provider-verified 2-dose coverage for MMR vaccine among adolescents aged 13 to 17 years was 87.0%.7 Mumps outbreaks in 2006 and 2009–2010 represented outbreaks in high 2-dose populations, with the latter providing a unique opportunity to study the use of a third dose for mumps outbreak control. In 2006, despite continued high MMR vaccine coverage, the United States experienced the largest mumps outbreak in 2 decades, with 6584 reported cases (incidence 2.2/100 000 persons). The highest incidence occurred among persons aged 18 to 24 years (incidence 31.1/100 000 persons versus 8.4/100 000 persons among all other age groups combined), many of whom were midwestern college students who had received 2 doses of mumps-containing vaccine.8 In 2007 and 2008, there were 800 (incidence 0.27/100 000 persons) and 454 (0.15/100 000 persons) reported mumps cases, respectively.9 In both years, the 1-dose coverage with MMR vaccine among children aged 19 to 35 months was 92.1% to 92.3%;5 and the 2-dose coverage among adolescents aged 13 to 17 years was 88.9% to 89.3%.10 In 2009, the United States experienced the next largest mumps outbreak in 2 decades among highly vaccinated populations. On June 28, an 11-year-old US resident with a history of receiving 2 doses of MMR vaccine developed parotitis after returning from the United Kingdom, where a mumps outbreak was ongoing.11 During his infectious period, he attended a summer camp for Orthodox Jewish boys in New York state; subsequently, 25 cases occurred at the camp. When the camp ended and attendees returned to their homes, community transmission occurred, resulting in mumps outbreaks in multiple locations in northeastern United States, including Orange County, New York. Most cases were among members of Orthodox Jewish communities who had received 2 previous doses of MMR vaccine.

In Orange County, mumps cases were first reported in September 2009. By December 31, 2009, 392 mumps cases were reported to the Orange County Health Department (OCHD); 290 (74%) had received 2 doses of MMR vaccine. Adolescents aged 11 to 17 years accounted for 72% of cases; 92% had received 2 age-appropriate doses of MMR vaccine. Reported cases were concentrated in a single village that had its own schools. Village members had limited contact with neighboring villages. The high average household size in the affected community (5.7 versus the US national average of 2.6)12 created an environment for possible augmentation of transmission. As a result, the outbreak continued despite standard outbreak control measures (eg, isolation of cases and ensuring appropriate vaccination of contacts). The characteristics of the village and ongoing mumps transmission in a setting of high 2-dose MMR vaccine coverage provided a unique opportunity to evaluate the use of a third dose of MMR vaccine for mumps outbreak control. This report describes the impact of the third dose of MMR vaccine on the mumps outbreak.

METHODS

The affected village in Orange County had a population of 20 363 in 2010 and a median age of 10.6 years.13 The village is served by 4 schools. Health care is provided mainly by 4 physician practices.

Because a high proportion of the mumps cases were among students in grades 6 to 12, a school-based vaccination intervention was proposed. To be eligible, a school needed to provide evidence of ongoing mumps transmission in the 2 weeks preceding the vaccination intervention, conducted from January 19 to February 2, 2010, and to document high 2-dose mumps vaccine coverage among the students by using the Comprehensive Clinical Assessment Software Application.14 As part of standard mumps outbreak control, a dose of MMR vaccine was offered to all students who had 0 or 1 previous MMR doses. However, eligibility for the third dose study was determined by documented evidence of previous receipt of 2 MMR vaccine doses. Students were eligible to receive a third dose of MMR vaccine if they reported no history of mumps during the current outbreak and provided a signed consent from their parent or guardian and their own written assent before vaccination. Validation of receipt of 2 previous doses of MMR vaccine was conducted by reviewing school vaccination records and, if missing, by contacting the student’s physician.
Because a third dose of MMR vaccine is not recommended by the ACIP, this study was reviewed and approved by the Institutional Review Boards at the Centers for Disease Control and Prevention and the New York State Department of Health.

**Mumps Case Ascertainment and Estimation of Third Dose Vaccination Coverage**

Mumps reporting is mandatory in New York.\(^{15}\) We ascertained mumps cases from 2 sources: notifications to OCHD and surveys of parents and guardians in the eligible schools. Reported cases were investigated to obtain additional epidemiological, clinical, laboratory, and vaccination information. Only mumps cases with onset dates during the outbreak (September 1, 2009 to June 30, 2010) were included in our analyses. Mumps cases were classified by using the 2008 Council of State and Territorial Epidemiologists definitions.\(^{16}\) We checked for duplicate reports of cases in OCHD registry and our surveys. There were 3 participants in OCHD registry who did not report having mumps in the surveys; these were considered mumps cases in the analysis.

A baseline survey was distributed to all sixth- to 12th-grade students to collect information on demographic characteristics, vaccination history, mumps history, clinical features and complications of recent episodes of mumps, and health care provider information. Two months (ie, >2 incubation periods) after the vaccination intervention, we distributed a follow-up survey to all sixth- to 12th-grade students at participating schools, whether or not they had completed the baseline survey or received vaccine during the intervention. The self-report follow-up survey collected information on symptoms associated with mumps that occurred after the intervention, as well as local and systemic adverse events after the receipt of the third dose MMR vaccine.

**Statistical Analysis**

Mumps attack rates (ARs) were calculated for students who participated in the study and received a third dose. Three time periods were defined in relation to each student’s date of receipt of the third dose of MMR vaccine. We also calculated mumps ARs for the entire village. For the village analysis, 3 time periods were defined for all persons, irrespective of vaccination status. Because the vaccination intervention was limited to schools, dates of vaccination were not available for other village residents. Therefore, the 2-week vaccination period, January 19 to February 2, 2010, was excluded from the periods defined to analyze villagewide ARs. Data from the surveys were entered into Microsoft Access 2003 (Microsoft Corp, Redmond, WA) and deidentified data were analyzed in SAS 9.2 (SAS Institute Inc, Cary, NC). \(P\) values of <.05 were considered to indicate statistical significance.

**Mumps ARs Among Sixth- to 12th-Grade Students in the Participating Schools**

Among students in the participating schools who were eligible for vaccination and completed the survey, we calculated ARs during three 21-day time periods based on each student’s vaccination date; the 21-day time periods were based on the average mumps incubation period of 16 to 18 days, range, 12 to 25 days.\(^{17}\) The 3 time periods were: (1) “prevaccination,” the 21-day period before vaccination; (2) “postvaccination phase 1,” 21 days after vaccination; and (3) “postvaccination phase 2,” 21 days after postvaccination phase 1. We assumed that some of the cases in postvaccination phase 1 were among students who had been incubating the virus at the time of vaccination, whereas cases in postvaccination phase 2 were a result of exposures occurring after vaccination. For the purpose of this analysis, students who did not receive the vaccine were assigned a “vaccination date,” based on the vaccination dates of students of the same class, gender, and age. ARs were calculated as the number of new mumps cases occurring in each of the specified time periods, divided by the number of susceptible students. Susceptible students included only those who did not have mumps at the beginning of the specified time period of analysis. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated. Among students eligible for a third-dose MMR vaccination, we also calculated the incremental vaccine effectiveness (ie, the decline in risk of disease among students who received the third dose of MMR vaccine in comparison with students who had only received 2 doses) by using the formula (vaccine effectiveness = 1 — rate ratio).

**Mumps ARs Among All Age Groups Villagewide**

Villagewide ARs among residents were calculated by using OCHD mumps registry for three 21-day time periods defined around the vaccine intervention period (January 19 to February 2): (1) “preintervention,” the 21 days before the intervention period; (2) “postintervention phase 1,” 21 days after intervention period; and (3) “postintervention phase 2,” the 21 days after the postintervention phase 1. Because most of the sixth- to 12th-grade students were aged 11 to 17 years, ARs were calculated for this age group and other age groups defined as <5 years, 5 to 10 years, 18 to 24 years, and ≥25 years. ARs for each age group were calculated by using the village population of 20,363, according to the 2010 US Census.\(^{13}\) Relative declines in ARs after the intervention were compared.
between age groups with Poisson regression.

RESULTS

From June 1, 2009 through June 30, 2010, 3502 mumps cases related to the Northeast mumps outbreak were reported to the Centers for Disease Control and Prevention, of which 790 (22.6%) were from Orange County, New York. Three of the 4 schools in the village were eligible for this study; the fourth school reported no mumps transmission in the 2 weeks preceding the intervention. Ninety-eight percent of schoolchildren in the village attended these 3 schools. Among the eligible schools, the weighted 2-dose MMR vaccine coverage based on the Comprehensive Clinical Assessment Software Application was 94.3%; vaccination records were incomplete for the remaining 5.7% of students. The baseline survey was conducted concurrently with the vaccine intervention, whereas the follow-up survey was conducted April 5 to 18, 2010. Of the 2688 sixth- to 12th-grade students in the eligible schools, 2537 (94.4%) returned the baseline surveys and 2356 (87.7%) returned the follow-up surveys. Of the 2688 students, 2265 (84.2%) were offered an additional dose of MMR vaccine (either as a part of standard outbreak control or as part of the third-dose intervention; Fig 1); 1258 (55.5%) were females. Of the 2265 students, 2178 (96.2%) had a validated history of receiving 2 previous doses of MMR vaccine and were eligible for the third-dose intervention. Of the 2178 eligible students, 1755 (80.6%) received a third dose of MMR vaccine during the intervention. In the comparison of those who received a third dose of MMR vaccine and those who did not, the proportion of male students was similar, but vaccinated students were more likely to be from school B (the largest school) and slightly more likely to be in the upper grades (Table 1).

Mumps ARs Among Sixth- to 12th-Grade Students in the 3 Eligible Schools

Among sixth- to 12th-grade students who had no previous history of mumps, the overall AR during the 3-week pre-vaccination period was 4.9%; ARs were higher among males (6.99%) than females (3.25%, P < .001 for comparison; Table 2). Rates were higher in schools A (5.1%) and B (5.3%) than in school C (2.8%). The overall AR declined significantly (P < .001) from 4.9% in the prevaccination period to 1.55% during the postvaccination phase 1. The decline in the overall AR from postvaccination phase 1 to the postvaccination phase 2 was also statistically significant (P < .001; Table 2). There were no significant differences in ARs between males and females during the postvaccination phase 2 (0.00% for males versus 0.24% for females; Fisher exact P = .26).

During the postvaccination phase 1, the overall AR was similar in both vaccinated and unvaccinated students (1.60% and 1.67%, respectively) (Table 2). However, during the postvaccination phase 2, the AR was eightfold lower among vaccinated students (Table 2), although the difference was not statistically significant (0.06% vs 0.48%, respectively; RR: 0.12; 95% CI: 0.01–1.32; P = .097). The incremental effectiveness of the third dose of vaccine (vaccine effectiveness) was 88.0%, with a large CI that included 0 (95% CI: −31.9% to 98.9%).

Mumps ARs Among All Age Groups Villagewide

After the third-dose intervention, ARs fell substantially among all age groups in the village (Fig 2). Overall, ARs villagewide declined from 0.86% during the 3-week preintervention period to 0.21% during the 3-week postintervention phase 2, a 75.6% relative decline (Table 3). This decline was statistically significant only among 11- to 17-year-olds (96.0% relative decline) and among 5- to 10-year-olds (72.9% relative decline). The relative decline in ARs in the 11- to 17-year age group was significantly greater (P < .005) than that in any of the other 4 age groups.

Self-reported Adverse Events After Immunization

Of the 1755 individuals who received the third dose of MMR vaccine, 1597 (91.0%) returned the follow-up survey. Of those, 115 (7.2%) reported at least 1 local or systemic adverse event in the 2 weeks after vaccination. The most commonly reported adverse events were “pain, redness, or swelling at the injection site” (3.6%) and “joint or muscle aches” (1.8%). No serious adverse events were reported in the survey, and a search of local physician records revealed no serious adverse events among the affected age groups.

DISCUSSION

This is the first documented study to assess the impact of a third dose of MMR vaccine on the course of a mumps outbreak in a highly vaccinated population, in which standard outbreak response measures had not been effective in halting the outbreak. After the intervention, there was a reduction in cases in all age groups, but this decline was particularly prominent and rapid among the older students (11–17 years of age) targeted for vaccination. The proportions of adverse events reported in this study were lower than or within the range of those in previous reports of first- and second-dose MMR vaccine studies. The circumstances of this outbreak response did not allow for the ideal evaluation of the effect of a third dose of vaccine, a randomized, placebo-controlled clinical trial. In addition, the intervention occurred immediately after the peak of the outbreak. For this reason, it is not possible to exclude the
possibility that the rapid decline in incidence after the intervention was entirely unrelated to our intervention. Declines in incidence were seen among 19.4% of students eligible for vaccination (but not vaccinated) after the intervention as well as among age groups not eligible for vaccination. However, the decline observed in the vaccinated age group (96.2% among 11- to 17-year-olds) was statistically significant, greater than that seen in any other age group. Furthermore, because transmission was particularly intense among the 11- to 17-year-olds, and such a large proportion of this group was vaccinated during the intervention, it is reasonable to expect the intervention to provide “herd-immunity” effects that would decrease incidence in nonvaccinated individuals. One would expect these effects to be most prominent among unvaccinated students in the same classes as the vaccinated students, as well as among 5- to 10-year-olds, the only other age group attending the same schools as the vaccinated children. After the intervention, incidence of mumps in this latter group fell by 72.8%, less than that observed in the vaccinated age group but more than that observed in any other age group.

Mumps-containing vaccines have been used for outbreak control among populations that were largely unvaccinated.\textsuperscript{17–21} In 1976, mumps vaccine was administered to a proportion of the population during an epidemic of mumps on St. Paul Island, Alaska, and transmission among vaccinees stopped approximately a month earlier than among those who were unvaccinated.\textsuperscript{19} Similarly, in 1986, at a time when only 1 dose of MMR vaccine was recommended in the United States, mumps vaccine was provided to 414 students and staff of a high school experiencing a mumps outbreak primarily among unvaccinated students.\textsuperscript{21} The authors concluded that the vaccination

### Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Students Who Did Not Receive a Third Dose (n = 423), n (%)</th>
<th>Students Who Received a Third Dose (n = 1755), n (%)</th>
<th>( \chi^2 )</th>
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<tbody>
<tr>
<td>School</td>
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<td>.0001</td>
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<td>School A</td>
<td>88 (21)</td>
<td>170 (10)</td>
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<tr>
<td>School B</td>
<td>249 (59)</td>
<td>1329 (76)</td>
<td></td>
</tr>
<tr>
<td>School C</td>
<td>96 (20)</td>
<td>256 (15)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
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<td>Females</td>
<td>234 (55)</td>
<td>986 (56)</td>
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<tr>
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<td>189 (45)</td>
<td>769 (44)</td>
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<tr>
<td>6–8</td>
<td>201 (48)</td>
<td>738 (42)</td>
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<tr>
<td>9–12</td>
<td>222 (52)</td>
<td>1017 (58)</td>
<td></td>
</tr>
</tbody>
</table>

\*Due to lack of documentation

Percentages are calculated based on the immediate preceding denominator

**FIGURE 1**

Study enrollment, sixth- to 12th-grade students in the 3 eligible schools, Orange County, New York, 2009–2010.
intervention may have had an impact on controlling the outbreak (postintervention \( RR = 0 \) [95% CI: 0–0.85]). Unlike these previous studies, this article assessed the use of a third MMR vaccine dose for outbreak control among a population with preexisting high 2-dose vaccine coverage.

Previous estimates of mumps vaccine effectiveness have ranged from 66% to 95% for 2 doses, consistently lower than estimates for measles vaccine effectiveness (95%–100%).

No data are available from this study regarding the immune response after a third MMR vaccine dose. Because of the high rate of vaccine uptake (80.6%) and the small number of cases (2 among the 413 unvaccinated students and 1 among the 1723 vaccinated students) that occurred >1 incubation period after vaccination, we are unable to directly evaluate the vaccine effectiveness. However, during this outbreak intervention, the rapid decline in incidence in the target age group suggests a rapid immune response to the third dose that resulted in relatively high mumps vaccine effectiveness. This finding is consistent with available data that demonstrated that a third dose of MMR vaccine administered to seronegative college students resulted in rapid mumps virus immunoglobulin G response, suggesting the capacity to mount an anamnestic immune response in previously vaccinated individuals.

Thus, a gap in protective efficacy as a result of suboptimal vaccine effectiveness, coupled with the potential for a rapid anamnestic immune response, supports the potential role of a third dose of a mumps-containing vaccine as an effective strategy for outbreak control in a setting of high 2-dose coverage.

Future mumps outbreaks are likely to occur among highly vaccinated populations, as seen in recent outbreaks in the United States and elsewhere.

Factors possibly contributing to these outbreaks include crowding, primary vaccine failure, suboptimal vaccine effectiveness, waning immunity, and the lack of natural boosting of mumps immunity by wild-type virus. The susceptibility of our study population was likely due to a high force of infection secondary to crowding, although waning immunity might be a factor as well. It is possible that the unusually large household size and crowding in the study halls at the religious schools may have augmented the transmission of mumps. A similar trend has been noted in previous mumps outbreaks in crowded prisons, orphanages, schools, and military facilities, as well as in the 2006 mumps outbreak, which affected mostly students in college dormitories.

While the use of a third dose of MMR vaccine may have been effective in limiting the size and duration of the outbreak described here, this finding should not support the routine use of a third dose of mumps vaccine in national vaccination programs. Although there were few mumps cases after the intervention because of the high uptake of the vaccine in the targeted age group, the results of our study suggest that...
administration of a third dose of MMR vaccine may be an effective method of controlling mumps outbreaks among highly vaccinated populations in certain settings. With the changing mumps epidemiology and limited options for outbreak control, additional studies to verify these findings in other settings are warranted. In addition vaccine immunogenicity studies in a highly vaccinated population receiving a third dose is of potential value to aid in understanding the kinetics of the immune response. Future studies should also attempt to better understand the dynamics of mumps immunity, as well as the biological correlates of protection afforded by the current vaccine.

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REFERENCES


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