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Effectiveness of a Third Dose of MMR Vaccine for Mumps Outbreak Control

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Abstract

BACKGROUND—The effect of a third dose of the measles-mumps-rubella (MMR) vaccine in stemming a mumps outbreak is unknown. During an outbreak among vaccinated students at the University of Iowa, health officials implemented a widespread MMR vaccine campaign. We evaluated the effectiveness of a third dose for outbreak control and assessed for waning immunity.

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METHODS—Of 20,496 university students who were enrolled during the 2015–2016 academic year, mumps was diagnosed in 259 students. We used Fisher's exact test to compare unadjusted attack rates according to dose status and years since receipt of the second MMR vaccine dose. We used multivariable time-dependent Cox regression models to evaluate vaccine effectiveness, according to dose status (three vs. two doses and two vs. no doses) after adjustment for the number of years since the second dose.

RESULTS—Before the outbreak, 98.1% of the students had received at least two doses of MMR vaccine. During the outbreak, 4783 received a third dose. The attack rate was lower among the students who had received three doses than among those who had received two doses (6.7 vs. 14.5 cases per 1000 population, P<0.001). Students had more than nine times the risk of mumps if they had received the second MMR dose 13 years or more before the outbreak. At 28 days after vaccination, receipt of the third vaccine dose was associated with a 78.1% lower risk of mumps than receipt of a second dose (adjusted hazard ratio, 0.22; 95% confidence interval, 0.12 to 0.39). The vaccine effectiveness of two doses versus no doses was lower among students with more distant receipt of the second vaccine dose.

CONCLUSIONS—Students who had received a third dose of MMR vaccine had a lower risk of mumps than did those who had received two doses, after adjustment for the number of years since the second dose. Students who had received a second dose of MMR vaccine 13 years or more before the outbreak had an increased risk of mumps. These findings suggest that the campaign to administer a third dose of MMR vaccine improved mumps outbreak control and that waning immunity probably contributed to propagation of the outbreak. (Funded by the Centers for Disease Control and Prevention.)

In the united states, immunization with two doses of the measles–mumps– rubella (MMR) vaccine as part of a childhood vaccination program led to a 99% reduction in reported cases of mumps by 2005.[1,2] Yet cases continue to occur annually, including outbreaks with thousands of cases reported in 2006, 2009, 2010, 2016, and 2017.[2-4] Many mumps outbreaks have occurred in college settings among students in whom rates of two-dose coverage have often exceeded 90%.[5,6] Contributing factors include waning of vaccine-induced protection, a two-dose MMR vaccine effectiveness of 66 to 95% against mumps, and accumulation of susceptible young persons who are brought together in high-density settings, which leads to a high force of infection and increased risk of exposure.[2,7-15]

State and local health departments often consider conducting MMR vaccination campaigns to control outbreaks, even in populations with high rates of two-dose coverage,[5,6,16,17] but limited data exist on the effect of a third MMR dose.[16,17] Determining the ideal target population for the intervention is difficult when cases are spread throughout a university setting with students living in close quarters, interacting socially, and attending classes together, so widespread third-dose interventions can be extremely time-consuming and resource-intensive.[17-19] Previous efforts to examine the effect of a third dose of MMR vaccine for outbreak control have suggested benefit, but data have been inconclusive.[16,17] The need for additional data with respect to the vaccine effectiveness of a third MMR dose to control mumps outbreaks is critical to inform vaccine-policy deliberations, as well as to provide effective public health guidance.

In the summer and fall of 2015, a mumps outbreak was reported at the University of Iowa, which requires that students receive two doses of the MMR vaccine before registration in spring semester classes. The university held eight mass- vaccination clinics on campus that targeted students younger than 25 years of age for a third dose of MMR vaccine. We evaluated the incremental effectiveness of a third dose of MMR vaccine during the outbreak and assessed whether waning immunity of the second vaccine dose played a role in the propagation of the outbreak.

METHODS

OUTBREAK SETTING AND IMMUNIZATION COMPLIANCE

The University of Iowa, located in Johnson County, Iowa, enrolls approximately 22,000 undergraduates. This evaluation was restricted to the university student population: 67% of mumps cases in Johnson County were diagnosed among university students, whose provider-verified vaccination records were available electronically.[20]

The two-dose MMR vaccine requirement for University of Iowa students has been in place since 2012. Students submit vaccination records with a provider signature, and a medically trained reviewer uploads records of valid vaccination doses to the electronic database. To register for spring classes (in approximately mid-October), students must have received two doses of MMR vaccine or have provided documentation of a medical or religious exemption or evidence of positive titers. Vaccination records are not required for a small subgroup of students, including some part-time and off-campus students, and for those with previous military service.

DATA SOURCE AND DEFINITIONS AND STUDY OVERSIGHT

We obtained student vaccination and demographic records from the university and determined the status of probable or confirmed mumps cases from the outbreak investigation,[20] using the case definition of the Council of State and Territorial Epidemiologists. Students were included in the analysis if they were age-eligible for the vaccination campaign (between the ages of 18 and 24 years by the date of the first campaign) and were enrolled in the full 2015–2016 academic year. Students with positive titers or for whom vaccination records were not required by the university were excluded from the analysis.

The outbreak period that we analyzed aligned with the academic calendar year from August 24, 2015, through May 13, 2016. Although the outbreak investigation identified cases from July 2015, 96% of the cases occurred within the outbreak period,[20] which was selected to ensure analysis of a uniform cohort of students with similar behaviors and exposures. An “outbreak dose” was defined as a dose of MMR vaccine that was administered on any date during the outbreak period. The vaccination campaign was conducted in eight clinics that were held over a 10-day period, starting on November 10, 2015. MMR vaccine was offered university-wide and free of charge for students younger than 25 years of age during extended hours at centralized locations throughout the campus. Dose status and vaccine dates were

verified by manual review of records for students with fewer or more than two MMR vaccine doses on file and for those with closely spaced or implausible vaccination dates.

The Iowa Department of Public Health and the Centers for Disease Control and Prevention (CDC) determined that this study was public-health-practice nonresearch and was therefore not subject to review by an institutional review board. All the authors vouch for the completeness and accuracy of the data presented.

STATISTICAL ANALYSIS

We used Fisher's exact test to compare unadjusted attack rates according to dose status and years since the receipt of the second dose of the MMR vaccine, as calculated by subtracting the date of the second dose from the last day of the outbreak period. We used multivariable time-dependent Cox regression models to estimate the risk- adjusted vaccine effectiveness. The at-risk period for each student began on the first day of the outbreak period and ended on the date of symptom onset for students who contracted mumps or on the last day of the outbreak period for students who did not contract mumps.

We examined the following variables according to case and vaccination status: age on the first day of the campaign, sex, race, undergraduate status, study program, receipt of campaign dose, ages at receipt of the first two doses of MMR vaccine, and years since receipt of each dose. The categories for years since the second dose were determined after consideration of several options, as shown in detail in Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. All the variables were included in the model and removed by backward elimination if they were not significant until the most parsimonious model was achieved. A P value of less than 0.05 was considered to indicate statistical significance. Statistical interaction and correlation between variables were assessed.

For the analysis comparing three doses with two doses, we defined incremental vaccine effectiveness as the additional reduction in the rate of mumps infection among students who received three doses as compared with those who received two doses. The outbreak dose was treated as a time-varying covariate. Students entered the outbreak period with two MMR doses and were analyzed as two-dose recipients until a specified period of time after receipt of the third dose, at which point they were analyzed as three-dose recipients. On the basis of the mumps incubation period (which ranges from 12 to 25 days, with parotitis typically developing 16 to 18 days after exposure to the mumps virus) and the period after vaccination that is needed for a primary or secondary immune response, we developed four models, each of which specified immunologic protection beginning at 7, 14, 21, or 28 days after vaccination, to understand the influence of different postvaccination time periods on vaccine effectiveness.

To evaluate the effectiveness of two doses of vaccine versus no vaccine, we created a separate model with a shorter time frame for analysis, from the start of the outbreak to the date immediately before the start of the first campaign, to avoid differences in risk during and after the campaign. Vaccine effectiveness was calculated as 1 minus the hazard ratio times 100. Data were analyzed with the use of SAS software, version 9.3 (SAS Institute).

RESULTS

VACCINATION HISTORY

Of the 20,496 students, the majority had received doses of MMR vaccine that were administered between the ages of 12 months and 23 months for the first dose, between 4 years and 6 years for the second dose, and between 18 years and 24 years for the third dose (Fig. 1). Before the outbreak, 20,107 of the students (98.1%) had received two or more vaccine doses; after the outbreak, 5187 (25.3%) had received three or more doses (Table S1 in the Supplementary Appendix). Of the 19,705 students who had received no more than two doses before the start of the outbreak, 4783 (24.3%) received a third dose during the outbreak period; of the third doses, 4494 (94.0%) were received during the vaccination campaign.

MUMPS ATTACK RATE

In the entire cohort of 20,496 students, the overall mumps attack rate was 12.6 cases per 1000 population, with 259 students meeting the case definition during the outbreak period (Table 1, and Fig. S2 in the Supplementary Appendix). The attack rate was lower among the recipients of three doses than among the recipients of two doses (6.7 vs. 14.5 cases per 1000 population, $P<0.001$). In a separate analysis involving 20,393 students who had received at least two previous MMR doses, those who had received the second dose within 12 years had lower attack rates than did those who had received a second dose 13 years or more before the outbreak. The attack rate was 1.6 cases per 1000 population if the second dose had been administered within 2 years and 3.9 cases per 1000 population if the second dose had been administered within 3 to 12 years. The attack rate jumped to 11.3 cases per 1000 population among the students who had received a second dose 13 to 15 years earlier and to a rate of 17.6 cases per 1000 population among those who had received a second dose 16 to 23 years earlier.

RISK OF MUMPS

The final multivariable regression model included two covariates: receipt of the third dose of MMR vaccine as a time-varying covariate and the number of years since receipt of the second dose. With a postvaccination window of 28 days and after adjustment for the number of years since the second dose, receipt of the third vaccine dose during the campaign was associated with a 78.1% lower risk of mumps than receipt of a second dose (adjusted hazard ratio, 0.22; 95% confidence interval [CI], 0.12 to 0.39) (Table 2). In addition, there was a stepwise increase in the risk of mumps with increased time since the second dose. Students who had received the second dose of MMR vaccine 13 to 15 years before the outbreak had a risk of contracting mumps that was 9.1 times the risk among those who had received the second dose within 2 years, and students who had received the second dose 16 to 24 years before the outbreak had 14.3 times the risk.

VACCINE EFFECTIVENESS

The incremental vaccine effectiveness of the third dose versus the second dose ranged from 60.0% (95% CI, 38.4 to 74.0) at 7 days after vaccination to 78.1% (95% CI, 60.9 to 87.8) at

28 days after vaccination (Table 3). The probability of remaining mumps-free was higher with receipt of the third dose for all time periods after vaccination (Fig. 2, and Fig. S3 in the Supplementary Appendix).

The vaccine effectiveness of two doses versus no doses of MMR vaccine differed according to the years since the receipt of the second dose, with an effectiveness of 89.4% (95% CI, −2.5 to 98.9) among students who had received the second dose less than 13 years before the outbreak and 31.8% (95% CI, −388.9 to 90.5) among those who had received the second dose 13 years or more before the outbreak (P=0.002).

DISCUSSION

Our data show the incremental effectiveness of a third dose of MMR vaccine for mumps outbreak control. The vaccination campaign that was implemented during the University of Iowa mumps outbreak resulted in the receipt of a third dose of MMR vaccine by 1 in 4 targeted students and was associated with a 60 to 78% reduction in mumps risk. Most of the students had received their first and second doses of vaccine during childhood, according to the recommendations of the Advisory Committee on Immunization Practices, which resulted in a highly vaccinated population before the outbreak. However, students who had received the second dose of MMR vaccine 13 years or more before the outbreak had 9 to 14 times the risk of mumps as did those who had received the second dose more recently. These findings suggest that the extent of the outbreak was limited by routine vaccination and by a strict university requirement that all students receive two doses of MMR vaccine, although waning immunity probably contributed to the propagation of the outbreak.

The time frame for the development of an immune response after the third dose of MMR vaccine is not well defined, but seroconversion has been shown at 7 to 10 days, 1 month, and 2 to 3 months after administration.[21,22] Our finding of 61% incremental vaccine effectiveness of three doses over two doses at 7 days after vaccination suggests a benefit shortly after vaccination, which is probably due to an anamnestic immune response (or so-called booster response). However, given the incubation period for mumps and the time needed for the development of an immune response, the observed incremental vaccine effectiveness of 78% at 28 days after vaccination might better represent the association between the third dose and decreased mumps risk. One study reported a point estimate for the incremental effectiveness of a third dose of vaccine that was similar to ours: 88% for a 21-day window after vaccination but with wide confidence intervals crossing zero.[17]

Results from previous investigations of mumps outbreaks with campaigns to administer a third dose of MMR vaccine suggest that the intervention might augment outbreak control. Attack rates declined after the intervention in large outbreaks in a religious community in the Northeast, where 81% of more than 2000 persons who were targeted in the campaign received a third dose, and in Guam in 2009 and 2010, where 33% of more than 3000 eligible students received a third dose.[16,17] However, in each setting, the peak of the outbreak had already occurred by the time that the vaccination campaign was implemented, which complicated the assessment of the true effect of the third dose of vaccine versus the natural evolution of the outbreak. After a campaign in which more than 8000 students were

vaccinated during a 2015 outbreak at the University of Illinois at Urbana-Champaign in a target population of approximately 50,000 with an estimated 97% rate of two-dose coverage, there was a decline in cases after the campaign, followed by a second peak before the outbreak was declared over; however, no formal evaluation was conducted to determine whether the reduction was a result of recent vaccination.[5]

Unlike these previous studies, the campaign in our study began just before the highest peak of the outbreak, which allowed for contemporaneous comparison of three doses versus two doses of MMR vaccine. In addition, there was a control factor with respect to timing, because a sufficient number of cases occurred after the campaign had begun. By the start of the spring semester 2 months after the intervention, there was a substantial decline in the risk of mumps, and the last case was reported on July 11, 2016.

Since only one quarter of the student population that was targeted for the intervention received a third dose, it is notable that the outbreak declined rapidly. In addition to the effect of the third dose, other factors that probably contributed to outbreak control were an organized public health response, including strong coordination between health departments and the university, along with the implementation of standardized protocols for case detection, rapid testing, and isolation by the student health center and heightened student awareness and adherence to provider recommendations for isolation. In addition, the strict two-dose MMR vaccination policy had contributed to the administration of more than 1300 MMR vaccine doses in the 6 months before the campaign, which probably helped to reduce the size of the outbreak (Table S1 in the Supplementary Appendix). Thus, the third-dose intervention was one tool among others that assisted with control of the mumps outbreak in this highly vaccinated population.

In previous studies, estimates of the effectiveness of two doses of MMR vaccine versus no vaccination have ranged from 66 to 95%,[7,13-15,23-25] and our estimate of 89% for the effectiveness of a more recent dose (<13 years before the outbreak) is consistent with these findings. However, our 32% estimate of the effectiveness of the administration of a second dose of MMR vaccine 13 years or more before the outbreak is quite low and had confidence intervals that crossed zero. At the same time, the estimates of the effectiveness of an early second dose versus a recent second dose were significantly different from each other. In addition, attack rates increased with the years since the second dose of vaccine, and if the second dose of MMR vaccine had been received 13 years or more before the outbreak, the risk of mumps was more than nine times as high as the risk if the second dose had been received more recently, which suggests waning immunity from the second dose.

Waning immunity has been shown in several previous studies, through a decrease in mumps antibody titers years after vaccination, a decrease in vaccine effectiveness in older populations, or an increase in the odds of disease with time since vaccination.[7-12] Because the students in this outbreak were born in the 1990s, their exposure to circulating wild-type virus was probably minimal, given the level of mumps control achieved after the 1989 recommendation that two doses of MMR vaccine should be administered. Therefore, opportunities for boosting immunity from wild-type virus exposure might not have occurred. In 2015, 90.7% of U.S. adolescents between the ages of 13 and 17 years had received at

least two doses of MMR vaccine.[26] If the current coverage levels continue, there may be even fewer opportunities for boosting of immunity from natural exposure, which could result in breakthrough mumps cases even in highly vaccinated populations.

We did not investigate whether the routine administration of a third dose of MMR vaccine might be a potential solution to achieving further mumps control, so our findings are best interpreted in the short-term context of an outbreak; the longer-term benefit has not been extensively investigated. One study that examined the antibody response in young adults after the receipt of a third dose of vaccine showed significantly higher geometric mean titers at 1 month and at 1 year after vaccination than before vaccination, but the antibody titers at 1 year were lower than those at 1 month.[22] In addition to monitoring the burden of disease over time among the recipients of three doses versus two doses, future studies are needed to examine biologic correlates of protection over time in populations that have received a third dose versus those that have not.

There are limitations to this investigation. Our study was observational, with possibly unmeasured factors that could have led to either overestimation or underestimation of the vaccine effectiveness. For example, there could have been differential receipt of the third dose of MMR vaccine on the basis of risk or other healthseeking behavior; there were anecdotal reports that some students sought MMR vaccination after a friend or roommate had contracted mumps or after they had been urged by a parent to get vaccinated. If the recipients of a third dose had been more frequently exposed to mumps, the incremental vaccine effectiveness would be underestimated.

In order to address the possibility of other unmeasured factors affecting vaccine effectiveness, such as differential intensity according to age, we conducted sensitivity analyses in which the time since the receipt of the second dose of vaccine was included as a continuous and dichotomous variable and in narrower age groups; the effect of time since the second dose was consistent with the results in other analyses (Table S2 in the Supplementary Appendix). Also, to confirm that the differences in the effects of two doses of vaccine versus three doses were not driven by mumps cases that occurred among students who had received two doses before the campaign, we performed an additional analysis that began on the first date of the campaign and excluded previous mumps cases (Table S3 in the Supplementary Appendix). The significantly lower risk of mumps among recipients of three doses than among recipients of two doses was consistent with the results in other analyses, which supported the validity of our original findings.

In conclusion, in a mumps outbreak that occurred in a highly vaccinated population, a third dose of MMR vaccine may have been of value for outbreak control. Our data also showed the importance of waning immunity and of assessing the time since the last vaccination. Since 2012, the CDC has provided guidance[27] for health departments that are considering use of a third dose of MMR vaccine, including in settings with more than 90% two-dose vaccination coverage, in intense-exposure settings such as schools and correctional facilities, and in settings with high attack rates (>5 cases per 1000 population) and with ongoing transmission (>2 weeks). This evaluation provides additional data on the effectiveness of the third dose of MMR vaccine in stemming a mumps outbreak in a highly vaccinated

population of university students, findings that health departments may take into consideration for mumps outbreak control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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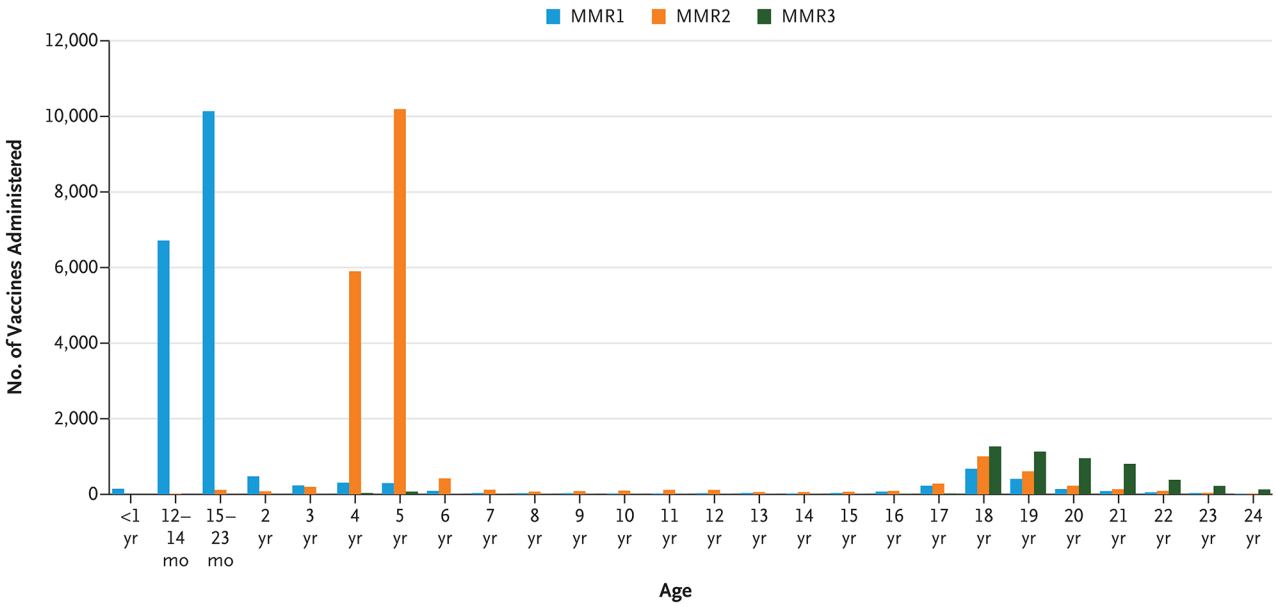

Figure 1. Age at the Time of Receipt of the Measles-Mumps-Rubella (MMR) Vaccine among Students Attending the University of Iowa (2015–2016).

Among the students who received a first dose of MMR vaccine (MMR1), 82.7% were vaccinated between the ages of 12 months and 23 months. Among those who received a second dose of MMR vaccine (MMR2), 81.6% were vaccinated between the ages of 4 years and 6 years. Among those who received a third dose of MMR vaccine (MMR3), 94.7% were vaccinated between the ages of 18 years and 24 years.

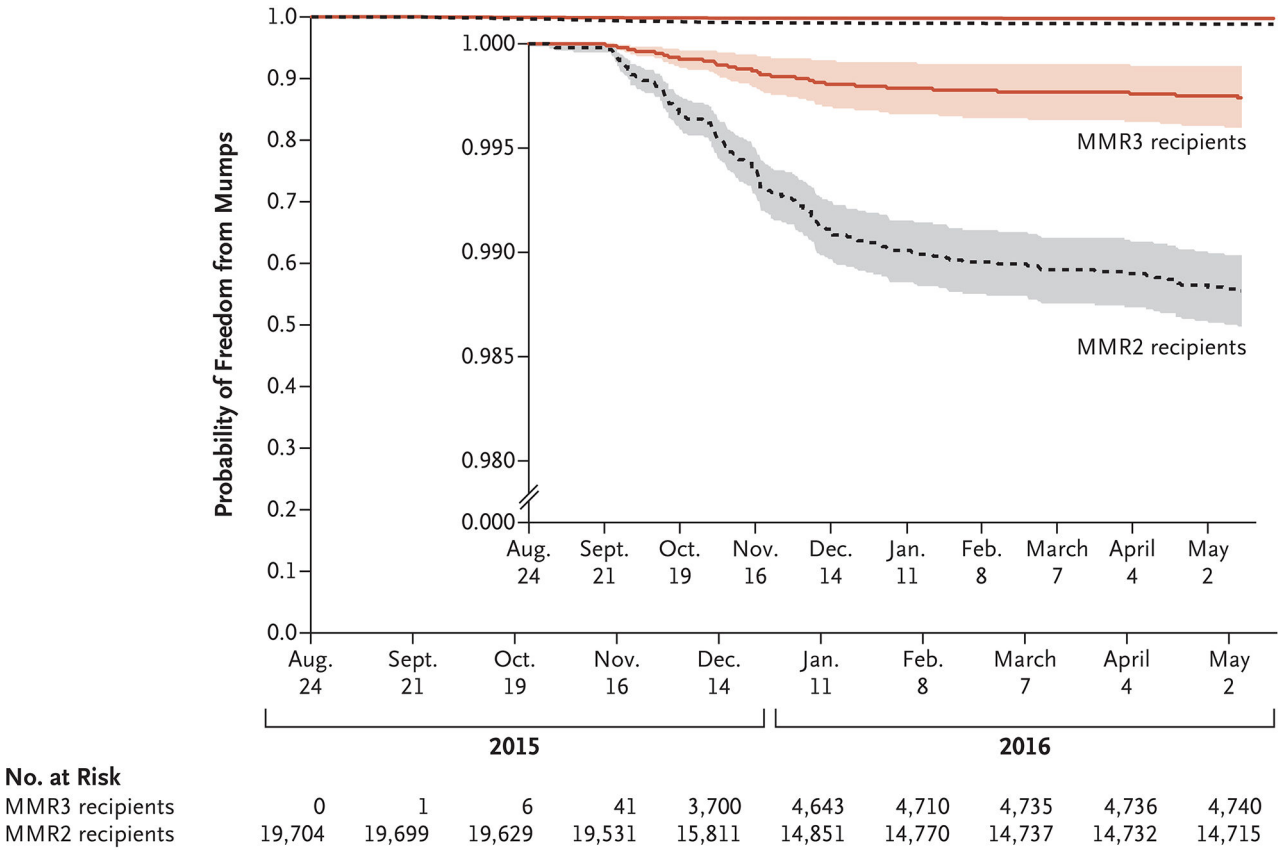

Figure 2. Probability of Freedom from Mumps among Vaccine Recipients of MMR3 versus MMR2.

The probability of remaining mumps-free was higher with receipt of the third MMR vaccine dose (MMR3) at 28 days after vaccination than with the second dose (MMR2). The inset shows the same data on an expanded y axis, with shaded areas indicating 95% confidence intervals. The data have been adjusted for the years since the receipt of MMR2. Graphs for models of data at 7 days, 14 days, and 21 days after vaccination are provided in Figure S3 in the Supplementary Appendix.

Table 1.

Mumps Attack Rates among Students at the University of Iowa (2015–2016).

Variable	Mumps Cases	* Population at Risk	Attack Rate	P Value†
	no. of students		*no./1000 population*	
All students	259	20,496	12.6	
No. of previous doses of MMR vaccine‡				<0.001
0	2	42	47.6	
1	2	61	32.8	
2	221	15,206	14.5	
3	34	5,110	6.7	
4	0	75	0	
5	0	2	0	
No. of years since receipt of MMR2§				<0.001
0–2	3	1,889	1.6	
3–12	5	1,293	3.9	
13–15	99	8,794	11.3	
16–23	148	8,417	17.6	

* Listed are the numbers of confirmed or probable mumps cases.

† P values were calculated to test whether the numbers in any subgroup differ from those in any other subgroup. P values were calculated with the use of Fisher's exact test.

‡ Listed are the numbers of doses of measles-mumps-rubella (MMR) vaccine that were administered before the onset of symptoms among the students who contracted mumps and at the end of the outbreak among those who did not contract mumps. The attack rates were calculated in the entire analyzed cohort of 20,496 students. When the analysis was limited to recipients of three doses of vaccine (MMR3) versus two doses (MMR2), the attack rate among MMR3 recipients was lower than that among MMR2 recipients (P<0.001 for the pairwise comparison).

§ In this category, attack rates were calculated in a subgroup of 20,393 students who had received at least two doses of MMR vaccine. A total of 103 students had not received MMR2 by May 14, 2016, including 3 students who contracted mumps.

Table 2.

Risk of Mumps among the Students Who Received MMR3 Vaccine, According to the Number of Days after Vaccination.*

Variable	7 Days after Vaccination		14 Days after Viccination		21 Days after Vaccination		28 Days after Vaccination	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Received MMR3		<0.001		<0.001		<0.001		<0.001
Yes	0.40 (0.26–0.62)		0.37 (0.24–0.58)		0.32 (0.20–0.51)		0.22 (0.12–0.39)	
No	Reference		Reference		Reference		Reference	
Time since MMR2 receipt		<0.001		<0.001		<0.001		<0.001
16–24 yr	14.3 (3.5–57.6)		14.3 (3.5–57.6)		14.3 (3.5–57.7)		14.3 (3.5–57.7)	
13–15 yr	9.1 (2.2–37.0)		9.1 (2.2–36.9)		9.1 (2.2–37.0)		9.1 (2.2–36.9)	
3–12 yr	3.1 (0.6–16.2)		3.1 (0.6–16.2)		3.1 (0.6–16.2)		3.1 (0.6–16.2)	
0–2 yr	Reference		Reference		Reference		Reference	

* The multivariable regression model included two covariates: receipt of the third dose of MMR vaccine (MMR3) as a time-varying covariate and the number of years since receipt of the second dose (MMR2). Each postvaccination window (7 days, 14 days, etc.) represents results from separate models, with each model analyzing the same set of students, and defines the point in time in which a student who receives a dose of vaccine moves from the two-dose group to the three-dose group. All P values were calculated with the use of the Wald chi-square test for overall effect.

Table 3.

Incremental Vaccine Effectiveness of MMR3 versus MMR2.*

Days after Vaccination with MMR3	Mumps Cases		Effectiveness of MMR3 vs. MMR2	P Value
	2 Vaccine Doses	3 Vaccine Doses		
	no.		*% (95% CI)*	
7 Days	230	23	60.0 (38.4–74.0)	<0.001
14 Days	232	21	63.2 (42.3–76.5)	<0.001
21 Days	235	18	68.3 (48.6–80.4)	<0.001
28 Days	241	12	78.1 (60.9–87.8)	<0.001

*Each postvaccination window represents results from separate models, with each model analyzing the same set of students, and defines the point in time in which a student who receives a dose of vaccine moves from the two-dose group to the three-dose group. The effectiveness of MMR3 as compared with MMR2 was calculated on the basis of the hazard ratios for contracting mumps in each dose group. All P values were calculated with the use of the Wald chi-square test for overall effect.