Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Cardemil CV, Dahl RM, James L, et al. Effectiveness of a third dose of MMR vaccine for mumps outbreak control. N Engl J Med 2017;377:947-56. DOI: 10.1056/NEJMoa1703309

Supplementary Appendix

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Design, data gathering, data analysis, publishing, first draft

The study was designed by Cristina Cardemil, Patricia Quinlisk, Kathleen Wannemuehler, Howard Gary, Danny Feikin, and Manisha Patel.

The data were gathered by Lisa James, Jacob Riley, Patricia Quinlisk, Minesh Shah, and Cristina Cardemil.

The data were analyzed by Cristina Cardemil and Rebecca Dahl.

All authors vouch for the accuracy and completeness of the analyses: Mona Marin, Danny Feikin, Manisha Patel, Lisa James, Jacob Riley, Patricia Quinlisk, Minesh Shah, Cristina Cardemil, Rebecca Dahl, Kathleen Wannemuehler, and Howard Gary.

The manuscript was first drafted by Cristina Cardemil, and all authors decided to submit the manuscript for publication.

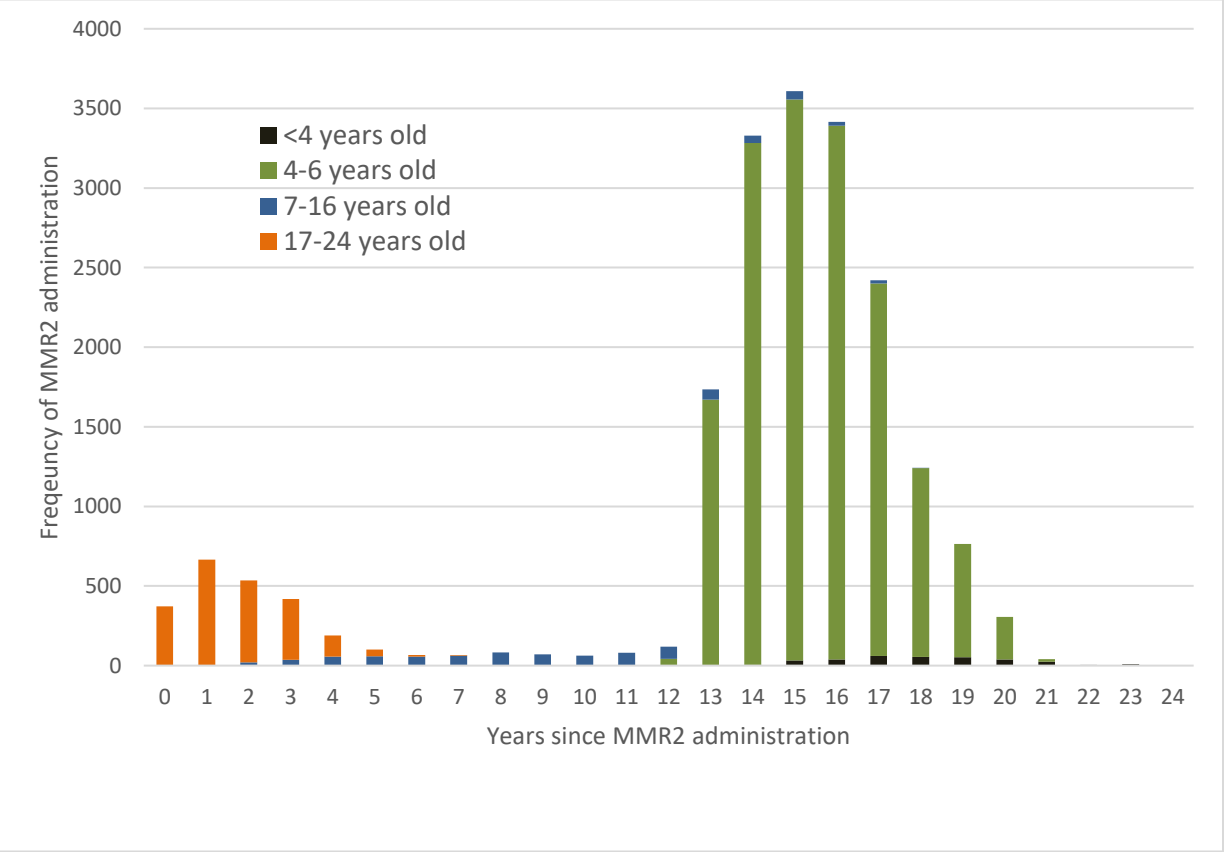
Table S1. Measles-mumps-rubella vaccine (MMR) coverage in students before and after outbreak period*, University of Iowa, 2015-2016

	Before outbreak period (August 23, 2015)		After outbreak period (May 14, 2016)	
MMR doses	**n**	**%**	**n**	**%**
0	123	0.6%	42	0.2%
1	266	1.3%	61	0.3%
2	19,705	96.1%	15,206	74.2%
3	377	1.8%	5,110	24.9%
4	25	0.1%	75	0.4%
5	0	0.0%	2	0.0%
Total	20,496		20,496	
2+ doses	20,107	98.1%	20,393	99.5%
3+ doses	402	2.0%	5,187	25.3%

* This table includes MMR coverage by dose status for students who were age-eligible for the vaccination campaign (18-24 years old by the date of the first campaign) and enrolled in the full 2015-16 academic year (n=20,496). Of all students enrolled at the University of Iowa in either the summer, fall or spring term of 2015-16 (n=33,783), 1,314 MMR doses were administered to 946 students in the six months prior to the campaign (May 1, 2015 to November 9, 2016).

Figure S1. Years since measles-mumps-rubella vaccine second dose (MMR2) receipt, by age at time of administration.

The distribution of the variable years since receipt of the second MMR dose (MMR2) was clustered in 2 periods (administration at 4-6 years of age as per the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices [ACIP] recommendations, and just prior to and during university enrollment at 17-24 years of age), with some students falling outside of the bimodal distribution.



Given this distribution, we examined years since receipt of MMR2 as a continuous variable, dichotomous variable (< 13 years and ≥ 13 years since receipt of MMR2), and categorical variable (0-2 years, 3-12 years, 13-15 years, and 16-24 years since receipt of MMR2). For the incremental VE 3 versus 2 doses analysis, regardless of the variable type used in the model, the result was statistically

significant ($p < 0.001$) (Table 2 and S2). Because the data are not linear—yet there is an increase in risk of disease with years since MMR2 administration—we report results in the manuscript using the categorical variable, in order to demonstrate this stepwise increase in risk. We also assessed for interaction between receipt of 3rd dose and time since receipt of MMR2; the standard error was very high for the interaction term and the outcome was not statistically significant, so this term was not included in the final model. For the 2 versus 0 doses analysis, because of the smaller sample size of the 0-dose group, this 4-level stratification was not possible, and we report results using the dichotomous variable.

Figure S2. Epidemic curve of confirmed and probable mumps cases in University of Iowa students, August 24, 2015-May 13, 2016. The eight mass vaccination clinics were held over six days from November 10-19, 2015, just prior to and during the highest peak of the epidemic curve, and are indicated by the black arrows. Probable cases are shown in gray bars; confirmed cases are shown in blue bars.

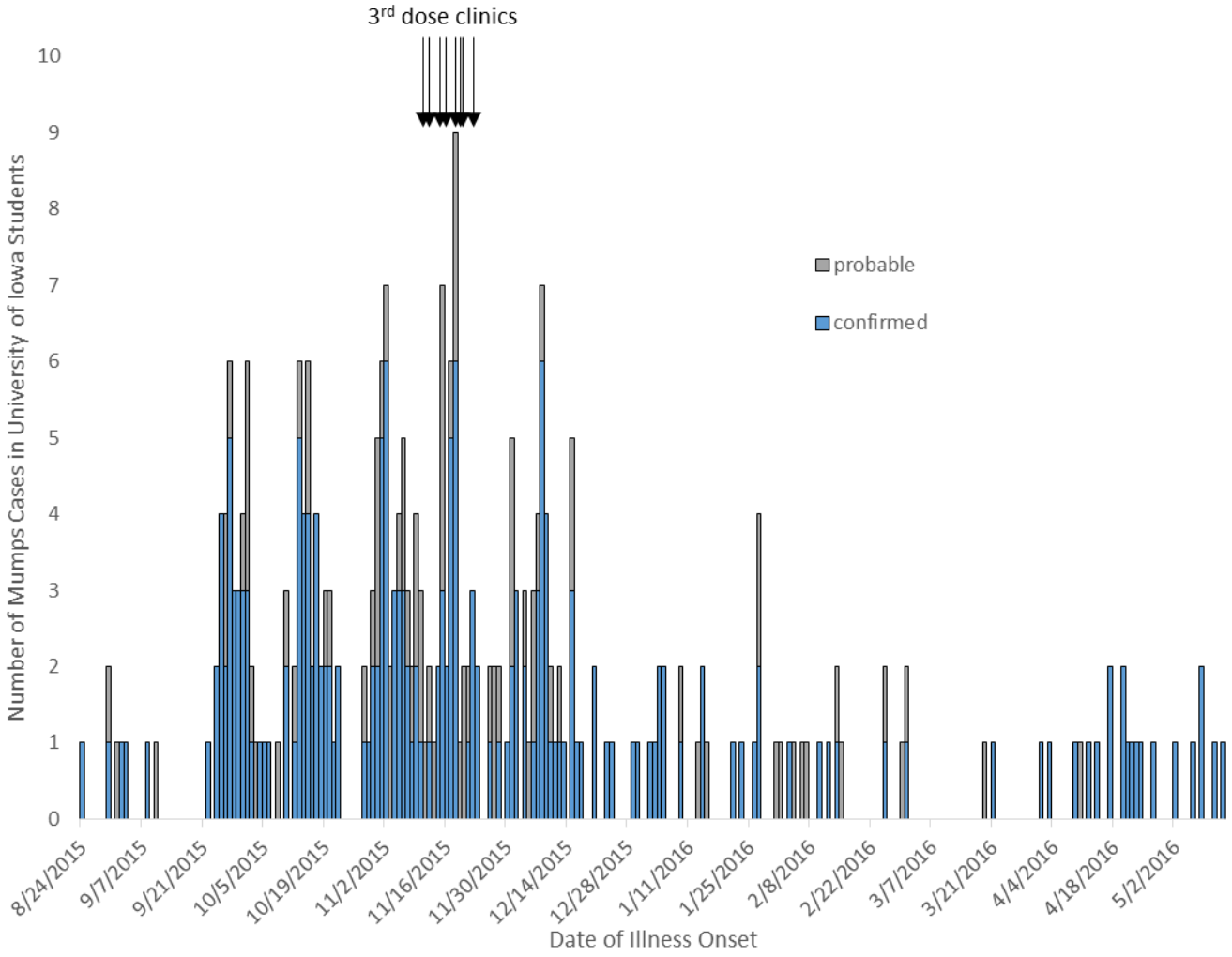
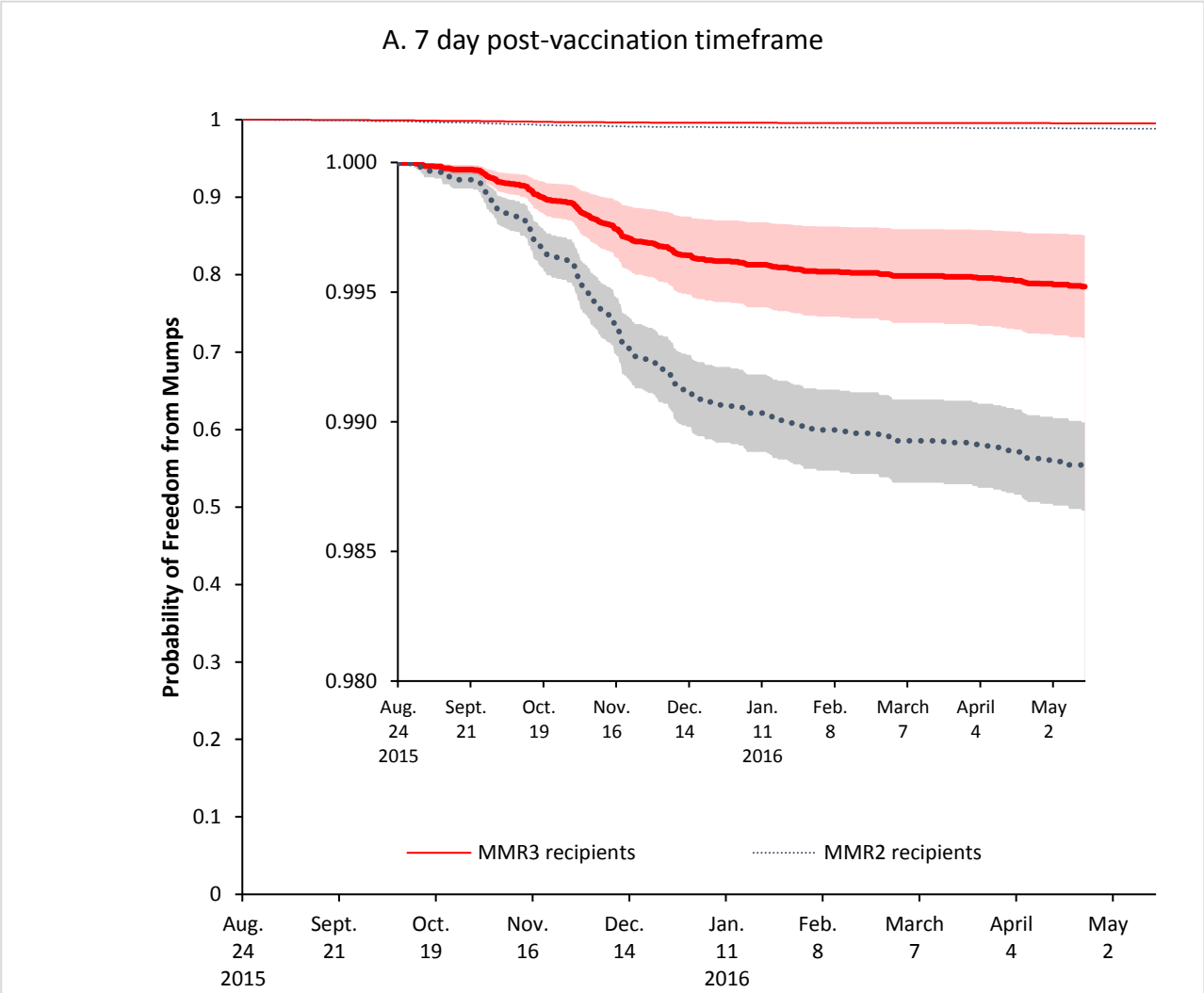


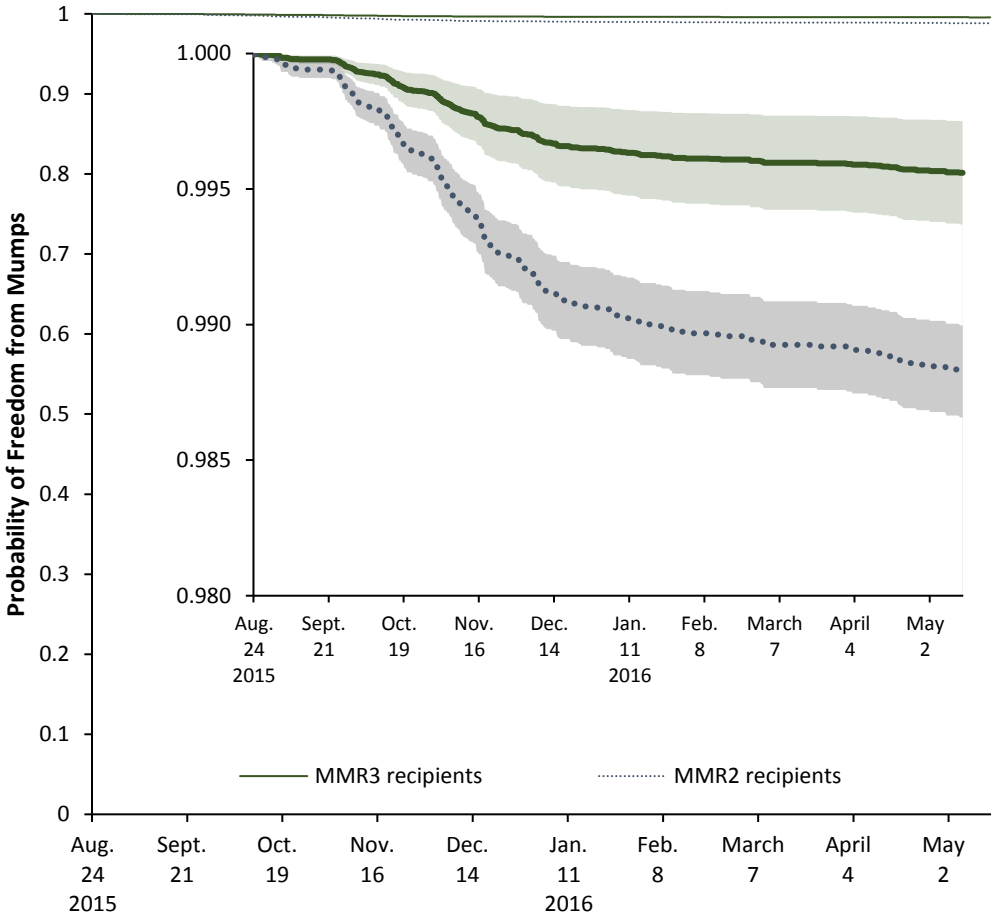
Figure S3. Mumps-free probability by receipt of the third measles-mumps-rubella (MMR) vaccine dose, for post-vaccination periods of 7, 14, and 21 days, University of Iowa, 2015-2016. The probability of remaining mumps-free was higher with receipt of the third dose for all time periods post-vaccination (panel A: 7-days; panel B: 14-days; panel C: 21-days post-vaccination). All models control for years since second MMR dose. 95% confidence bands shown in insets.



No. at Risk

MMR3 recipients	0	3	40	79	4,605	4,714	4,734	4,737	4,737	4,735
MMR2 recipients	19,704	19,697	19,595	19,493	14,906	14,780	14,746	14,735	14,731	14,720

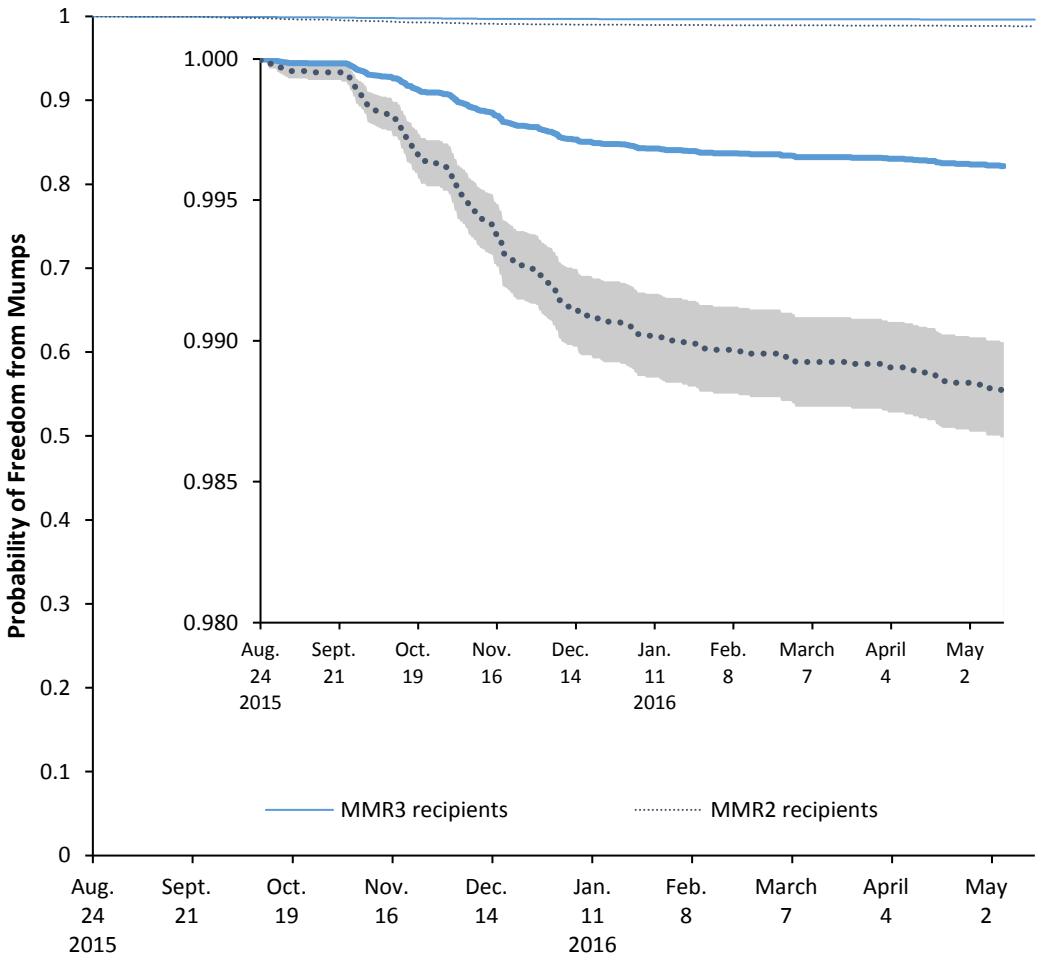
B. 14 day post-vaccination timeframe



No. at Risk

MMR3 recipients	0	2	12	61	4,563	4,712	4,732	4,737	4,737	4,737
MMR2 recipients	19,704	19,698	19,623	19,511	14,948	14,782	14,748	14,735	14,731	14,718

C. 21 day post-vaccination timeframe



No. at Risk

MMR3 recipients	0	1	8	57	4,548	4,697	4,732	4,737	4,737	4,737
MMR2 recipients	19,704	19,699	19,627	19,515	14,963	14,797	14,748	14,735	14,731	14,718

Table S2. Reduction in Mumps in Third Dose MMR Recipients and Effect of Time Since MMR2: Results of Sensitivity Analyses in Narrower Age Groups, and with Years since MMR2 as a Dichotomous and Continuous Variable, University of Iowa, 2015-16

	Model 1		Model 2		Model 3		Model 4	
	Age Group: 20-22 years old		Age Group: 19-21 years old		Years Since MMR2 as a Dichotomous Variable		Years Since MMR2 as a Continuous Variable	
Variable	**Hazard Ratio (95% CI)[1]**	**p-value[2]**	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Received third MMR dose[3]		< 0.001		< 0.001		< 0.001		< 0.001
Yes	0.16 (0.07, 0.39)		0.10 (0.04, 0.28)		0.22 (0.12, 0.39)		0.22 (0.12, 0.39)	
No	REF		REF		REF		REF	
Years since MMR2		< 0.001		< 0.001		< 0.001		< 0.001
13-24	8.8 (2.8, 27.7)		9.2 (2.9, 28.9)		6.0 (2.8, 12.6)		1.15 (1.09, 1.22)	
0-12	REF		REF		REF			

1- 95% Hazard Ratio Confidence Limits.
2- All p-values are Wald Chi-Square Type 3 for overall effect.
3- 28 day post-vaccination timeframe for all models

Table S3. Reduction in Mumps in Students Who Received a Third MMR Dose, Excluding Cases Prior to Campaign*, University of Iowa, 2015-16

Time period post-vaccination	Incremental Vaccine Effectiveness (3 vs 2 doses)	95% Confidence Interval	p-value
7 days	37.9%	2.3, 60.5	0.04
14 days	43.1%	9.0, 64.5	0.02
21 days	52.1%	21.0, 71.0	0.004
28 days	68.2%	42.2, 82.5	<0.001

*Person-time began on November 10, 2015, the first date of the MMR campaign. All cases prior to the campaign (n=117) were excluded from analysis, resulting in 136 cases remaining among 19,588 2-dose recipients.