



Update on Mumps Epidemiology in the United States, 2017 and Review of Studies of 3rd Dose of MMR Vaccine

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CDC

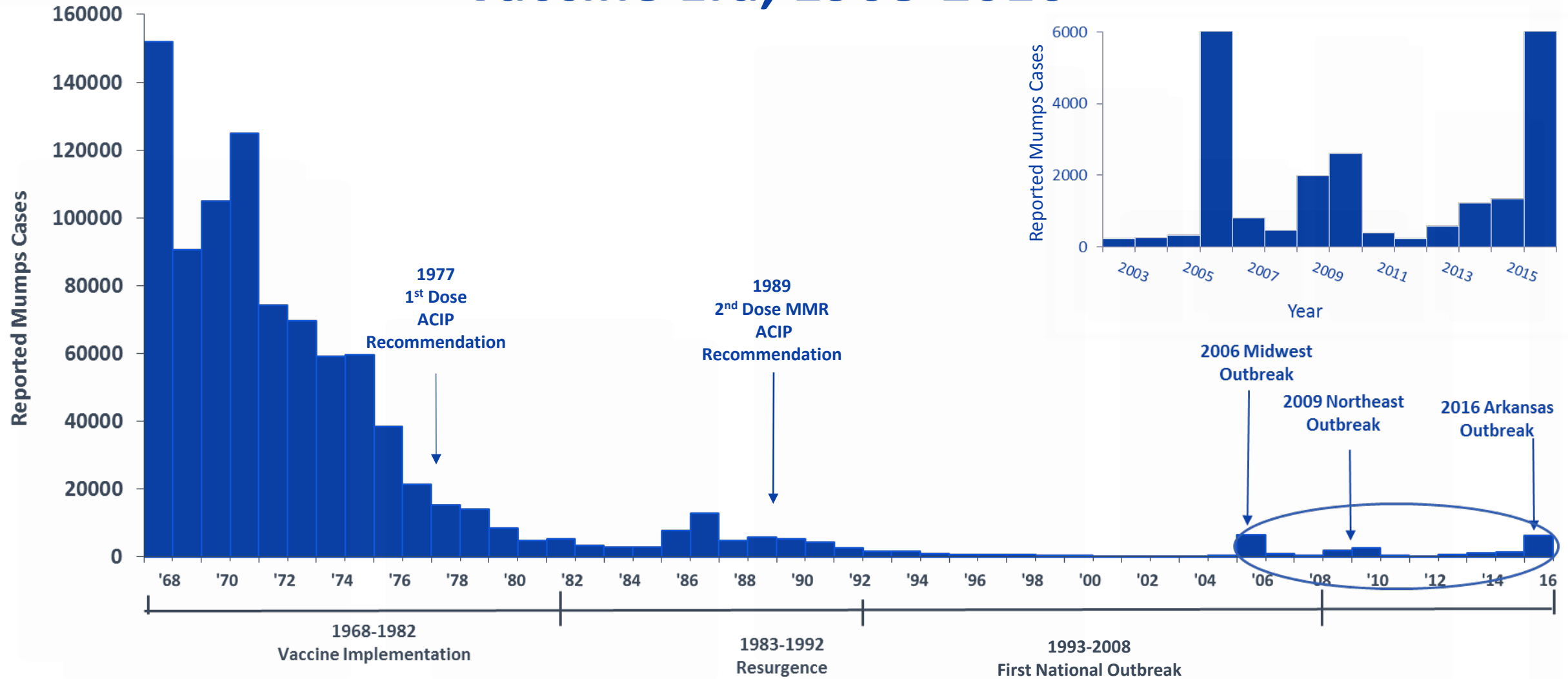
ACIP Meeting

June 22, 2017

Presentation Outline

- Update on mumps epidemiology in the United States in 2017
- Evidence reviewed by the Mumps Work Group concerning
 - Immune response to the 3rd dose of measles, mumps, rubella vaccine (MMR3)
 - Published studies on use of MMR3 for mumps outbreak control
 - Safety of MMR3
- *Work Group deliberations and interpretation of the evidence on use of MMR3 are ongoing and will be presented during the October ACIP meeting*

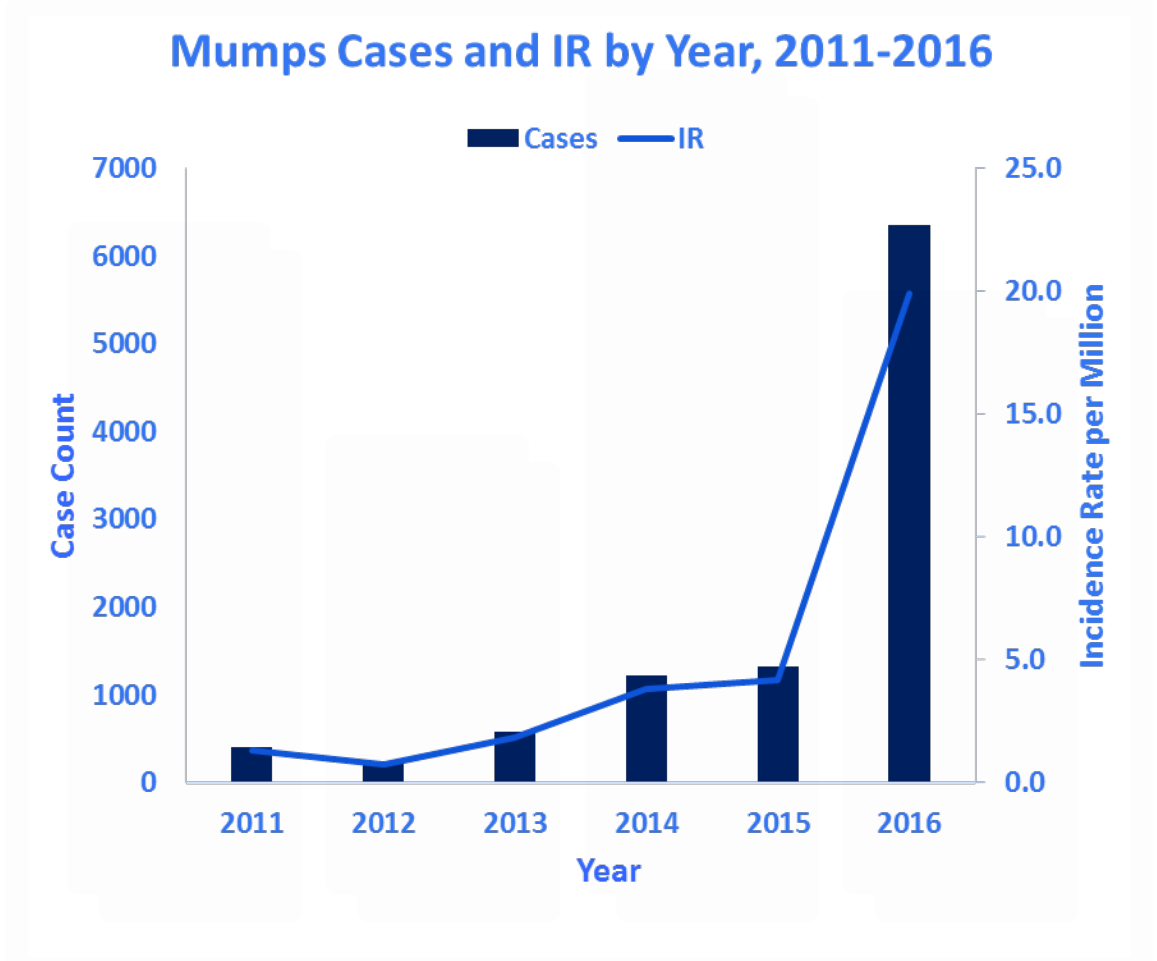
Reported Mumps Cases, United States, Vaccine Era, 1968-2016



Source: National Notifiable Diseases Surveillance System (passive surveillance); 2016 data is preliminary (May 31, 2017) and subject to change

Mumps Cases, Incidence Rate (IR) and Outbreak (OB)-Related Data, United States, 2011-2016

	2011	2012	2013	2014	2015	2016
Case Count	404	229	584	1223	1329	6353
I.R.	1.3	0.7	1.9	3.8	4.2	19.9
OB Cases	128	3	313	747	836	4975
% of OB Cases	32	1.3	54	61	63	78
Jurisdictions w/OB cases	9	3	11	15	14	32

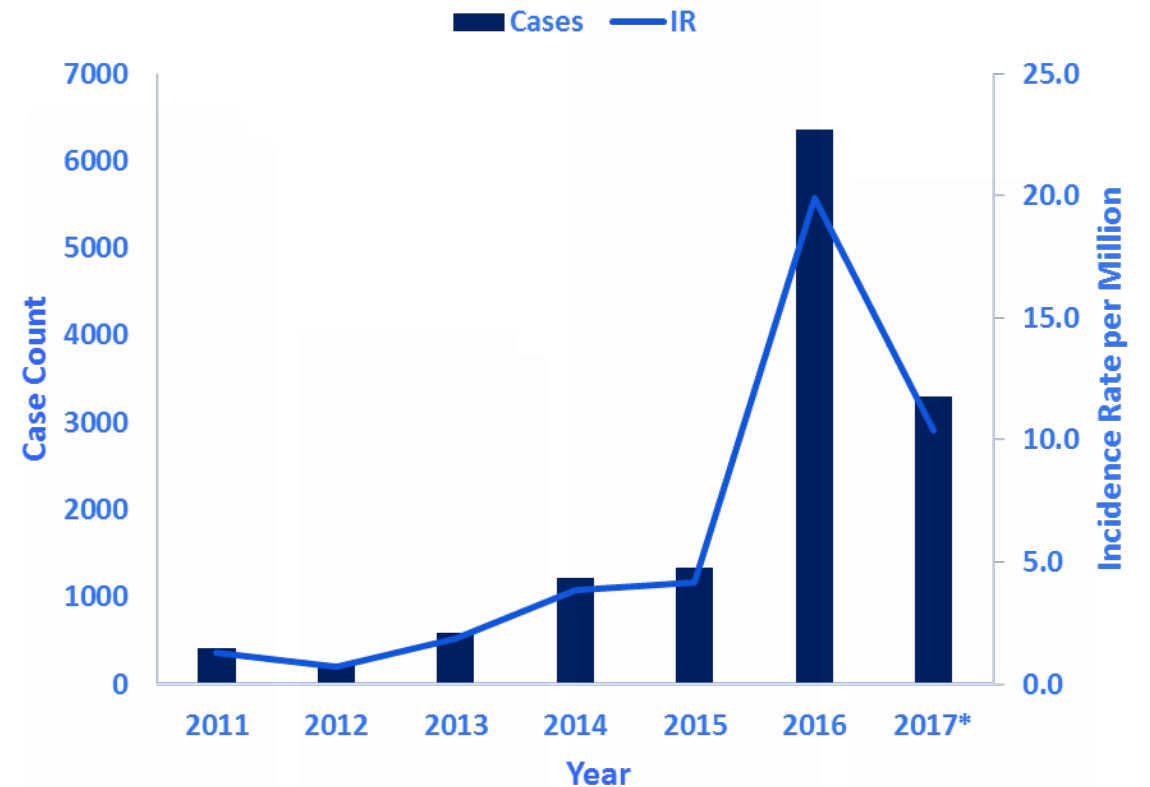


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IR	1.3	0.7	1.9	3.8	4.2	19.9	10.4
OB Cases	128	3	313	747	836	4975	2190
% of OB Cases	32	1.3	54	61	63	78	66
Jurisdictions w/OB cases	9	3	11	15	14	32	32

Mumps Cases and IR by Year, 2011-2017

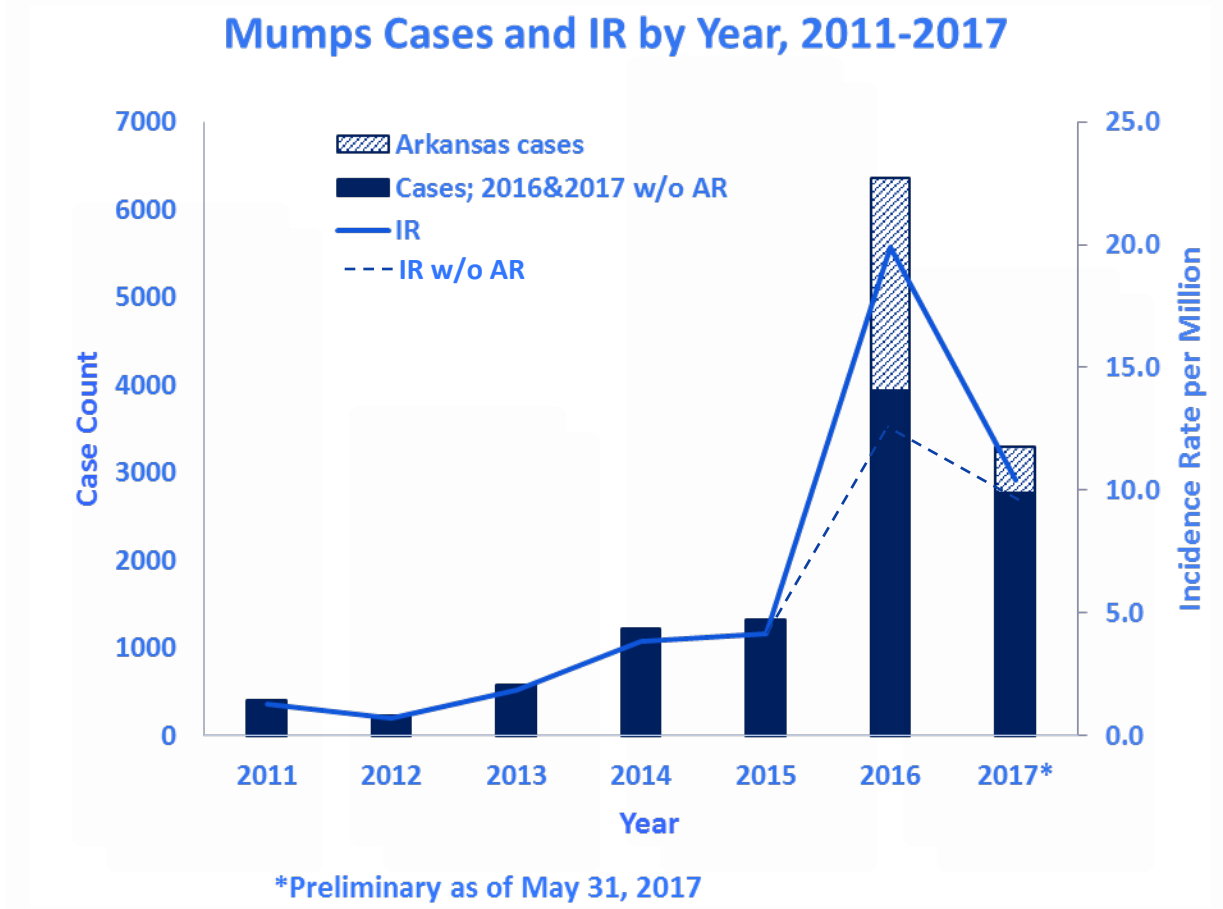


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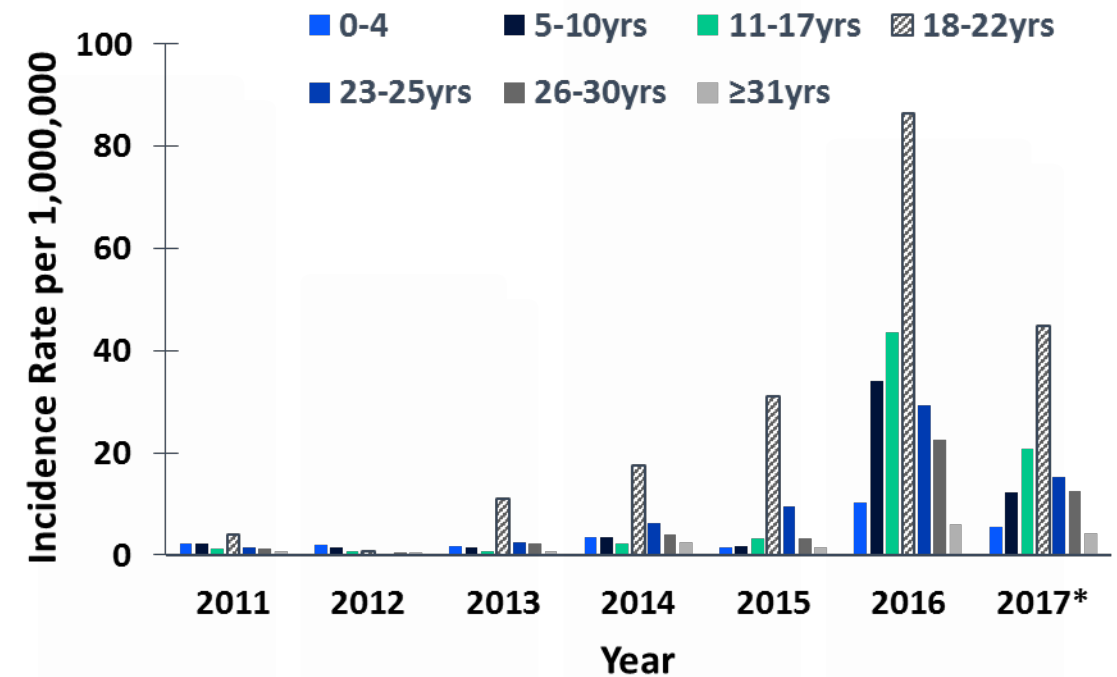


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Characteristics of Reported Mumps Cases and Outbreaks, United States, 2017*

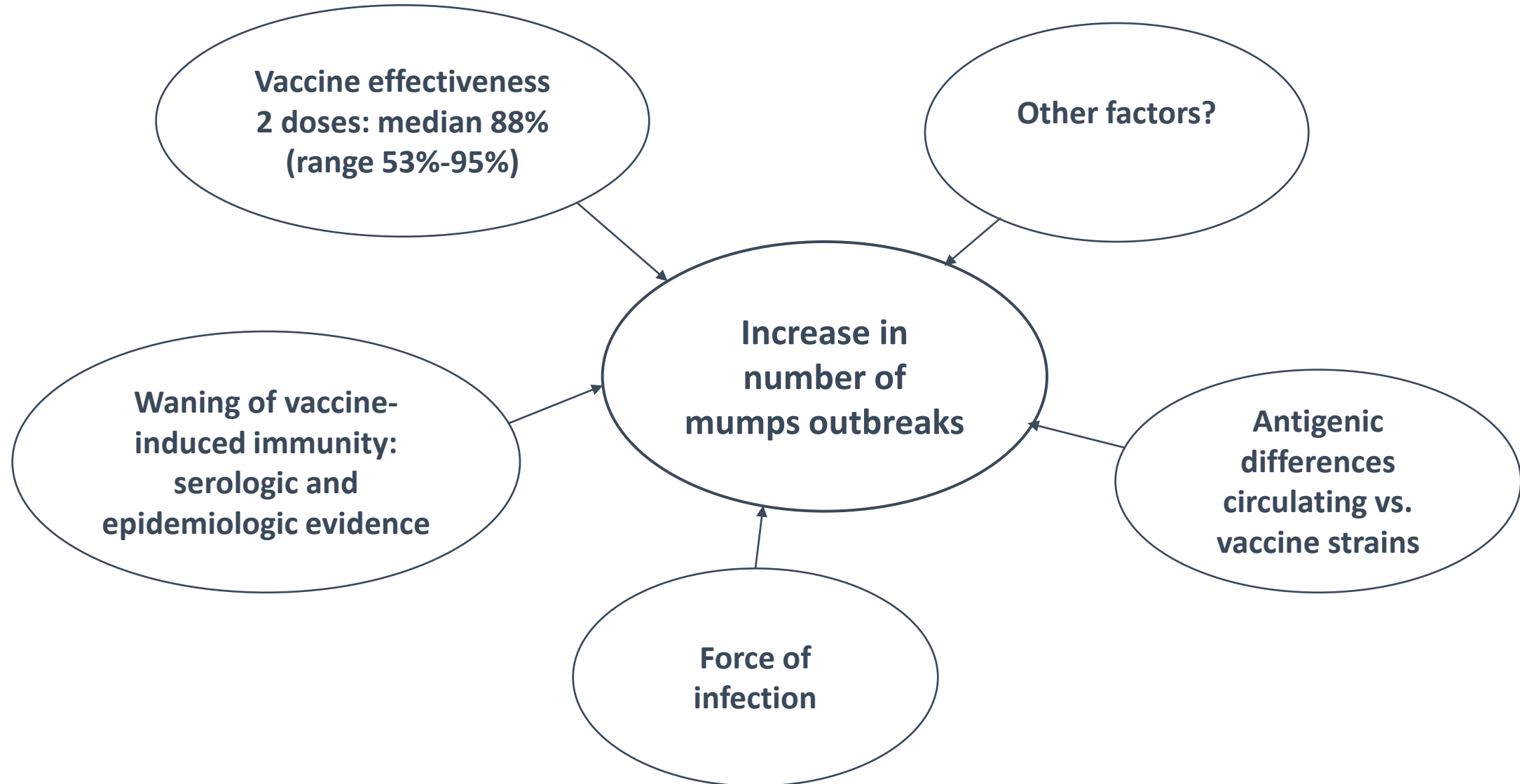
- Highest incidence: 18-22 age group
- Age: median=23 years, IQR=15-30 years
- Vaccination status: 73% ≥ 2 MMR doses
- Outbreaks: at least 40 known to CDC
 - 19 universities
 - 14 community-wide (9 in close-knit communities [8 in Marshallese communities])
 - 7 other close contact settings: prison [3], high school [2], military facility [1], hockey team [1]

Reported Mumps Incidence Rates by Year and Age Group, United States, 2011-2017



*Preliminary as of May 31, 2017

Factors that Might Contribute to the Increasing Number of Mumps Outbreaks



Studies of 3rd Dose of MMR Vaccine

- **Laboratory Evidence**
Laboratory Evidence

Mumps Antibody^a Before and After MMR3 Vaccination

- N=656 young adults
- Median age at MMR3=21 years
- Mean years since MMR2=15 (95% Confidence interval: 14.9-16)

	Baseline (pre-MMR3)	1-month after MMR3	1-year after MMR3
N	656	655	612
Geometric Mean Titers (95% CI)	104 (95, 114)	159 (147, 172) ^b	126 (115, 137) ^c
≥4-fold increase from baseline, n (%)	--	40 (6)	13 (2)
Negative or low titers^d, n (%)	43 (7)	10 (2)	19 (3)

^a Neutralizing antibody against Jeryl Lynn vaccine virus

^b p<0.0001 for comparison with baseline

^c p<0.01 for comparison with baseline

^d titers <16

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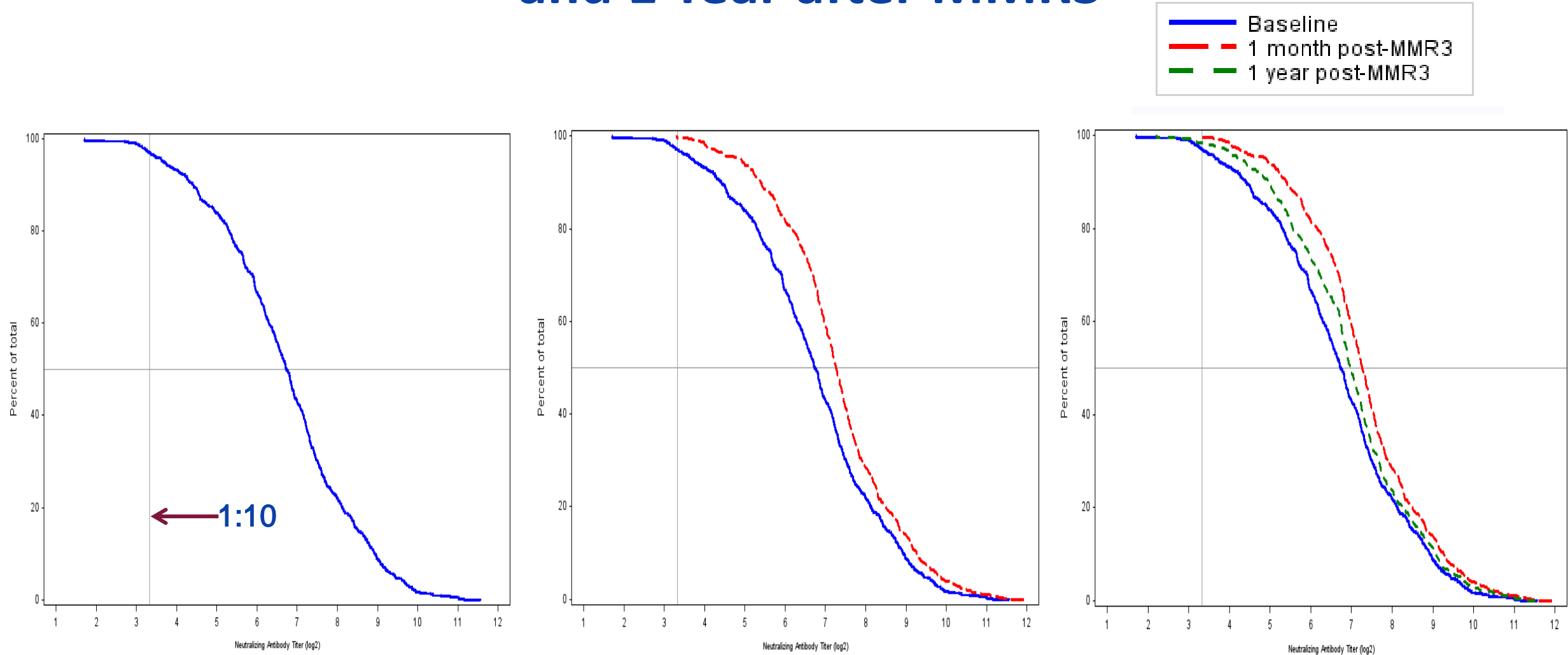
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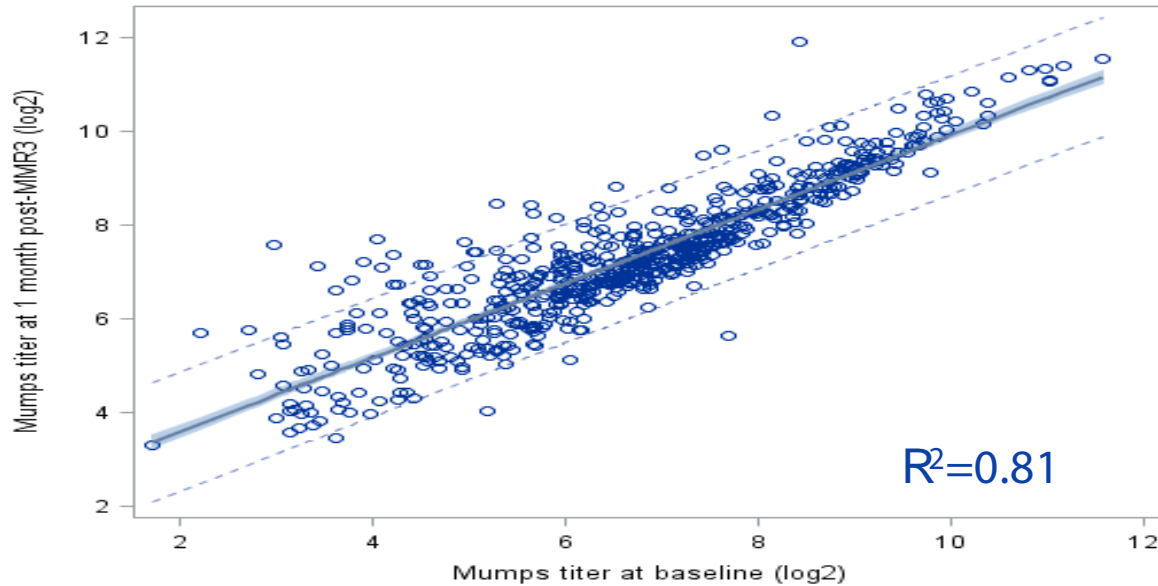
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Distribution of Mumps Antibody Titers: Baseline, 1 Month and 1 Year after MMR3

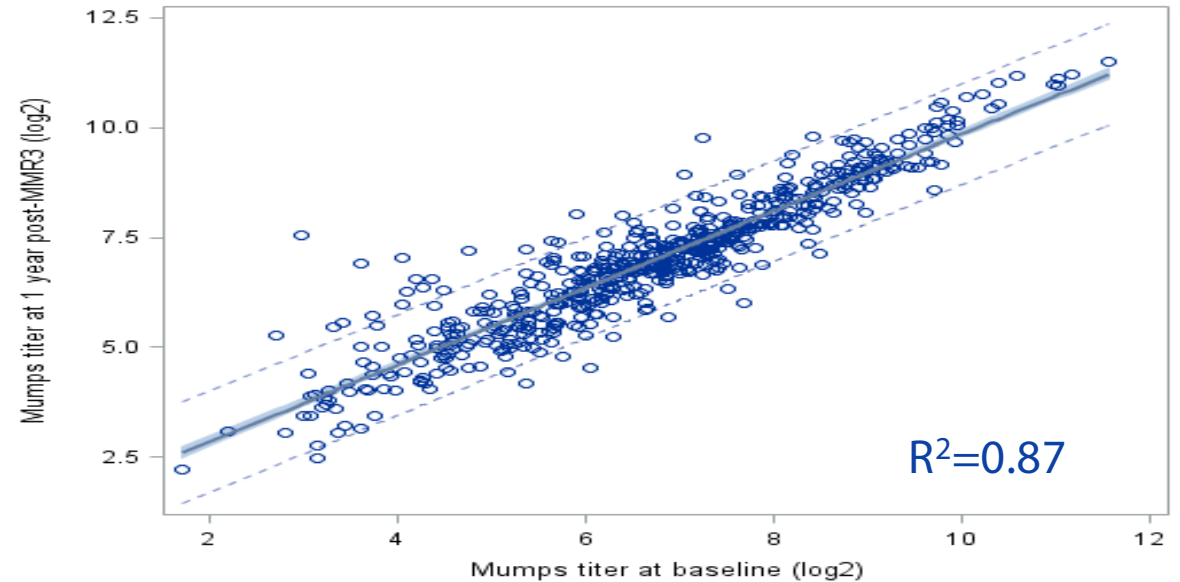


Post Vaccination Antibody Neutralizing Titer Highly Correlated with Baseline Titer

1 Month after MMR3 (n=655)



1 Year after MMR3 (n=612)



— Fit □ 95% Confidence Limits - - - 95% Prediction Limits

- Nearly identical findings observed when antibodies against mumps specific proteins (hemagglutinin [HN] or nucleoprotein [NP]) were studied
- An inherent trajectory for mumps titer or a set point for individual antibody levels that is minimally affected by MMR3

Antibody Response to MMR3

- 17 students and staff at the University of Nebraska age 19-30 years seronegative for mumps after MMR2 received MMR3
 - 91% developed an IgG response 2-3 months after MMR3
 - Response was rapid (observed at 7-10 days) with peak antibody activity between 7-10 days and 2-3 months
 - Antibody kinetics 2-3 months after MMR3 not evaluated

Laboratory Evidence on MMR3 Use

- Limitations
 - Limited evidence
 - No correlate of protection
 - The qualitative aspects of the immune response (antibody avidity, B-cell memory) or the strain specific immune response after MMR3 not assessed

Studies of 3rd Dose of MMR Vaccine

- **Epidemiologic evidence**
Epidemiologic evidence

Epidemiologic Evidence on MMR3 Use

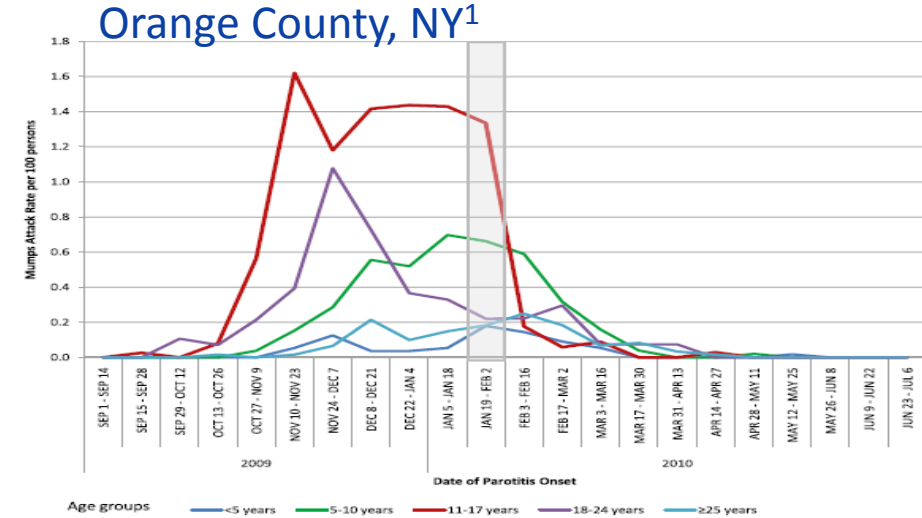
- 3 studies assessed the impact of MMR3 for mumps outbreak control
 - 2 school-based
 - Ogbuanu et al., *Pediatrics*, 2012 (Orange County NY)
 - Nelson et al., *Pediatr Infect Dis J*, 2013 (Guam)
 - 1 university setting
 - Cardemil et al., 2016 (unpublished data, next presentation)

MMR3 Use in Orange County, NY & Guam Outbreaks, 2009-2010

- Orange County: 81% of eligible students (age 11-17 years) received MMR3¹
- Guam: 33% of eligible students (age 9-14 years) received MMR3 ²
- Both studies: rates lower in MMR3 recipients than in MMR2 recipients; results not statistically significantly different, small number of cases post MMR3 intervention
 - Orange County: incremental effectiveness of MMR3: 88% (-31.9% to 98.9%)
- In Orange County attack rates fell postintervention among all age groups in the community with the highest (and significant) decline among 11-17 followed by 5-10 year-olds

MMR3 Use in Orange County, NY & Guam Outbreaks, 2009-2010

- Attack rates declined after MMR3 administration but the MMR3 intervention occurred after the peak of the outbreak and the possibility of the declines being unrelated to the intervention could not be excluded



The box indicates the period of the third MMR vaccine dose intervention

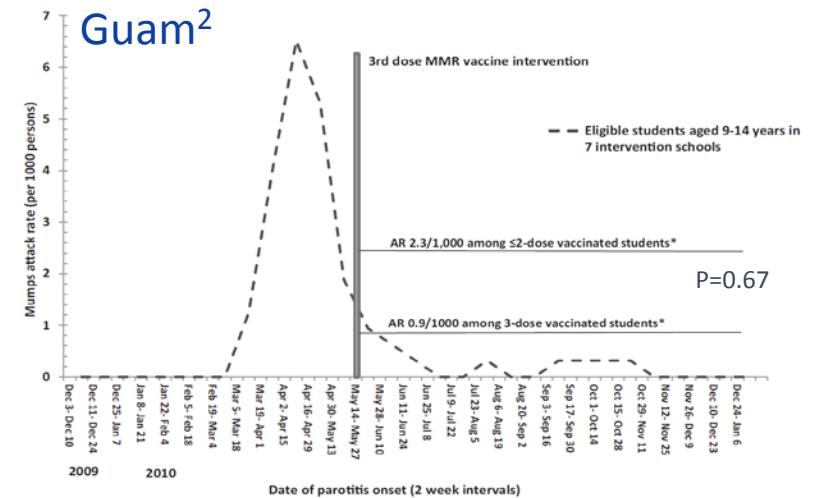


FIGURE 4. Comparison of mumps attack rates (cases/1000) postintervention among eligible students who received the third MMR vaccine dose compared with those who did not receive the third dose, Guam, December 1, 2009, to December 31, 2010. *More than 1 incubation period postintervention.

¹ Ogbuanu IU et al. *Pediatrics* 2012; ² Nelson GE et al. *Pediatr Infect Dis J* 2013

Safety Evidence

-

Studies of 3rd Dose of MMR Vaccines

Safety Evidence

MMR3 Vaccine Safety (Preliminary Data)

- 662 young adults received MMR3 and completed safety diaries (Marshfield Clinic)
- Solicited symptoms* 2 weeks before and 4 weeks after MMR3
- Significantly higher rate after vaccination vs. pre-vaccination: headache, joint pain, diarrhea and swollen glands
 - Low proportion of subjects, short duration of symptoms

Adverse event	% of subjects*	Median duration (days)
Headache	12	2
Joint pain	4	2
Diarrhea	6	1
Swollen glands	1.5	3

*crude proportion in the 4 weeks after MMR3, baseline rates of events not subtracted

- No serious adverse events requiring medical attention
- MMR3 appears safe and well tolerated in a young adult population

*Fever, runny nose, cough, red eyes, vomiting, diarrhea, jaw swelling, swollen glands, headache, rash, joint problems + redness, swelling, pain

Unpublished data, Janell Routh, MD (CDC) presentation to the Work Group, May 11, 2017.

Knowledge Gaps and Planned Studies

- Cost of public health response to contain a mumps outbreak in an university setting, including MMR3 intervention (University of Iowa, 2015-2016)
- Cost effectiveness analysis of various policy options for MMR3 to prevent or control mumps outbreaks
- Model the impact of MMR3 on burden of mumps during a mumps outbreak
- Genotype G strain specific immune response
 - To MMR3
 - To MMR2 >10 years
- More complete national data on epidemiology of and response to mumps outbreaks
- Question for ACIP: additional 3rd dose data that would be helpful to inform ACIP deliberations?

Acknowledgements

Manisha Patel

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Carole Hickman

Don Latner

Adria Lee

Mumps ACIP Work Group

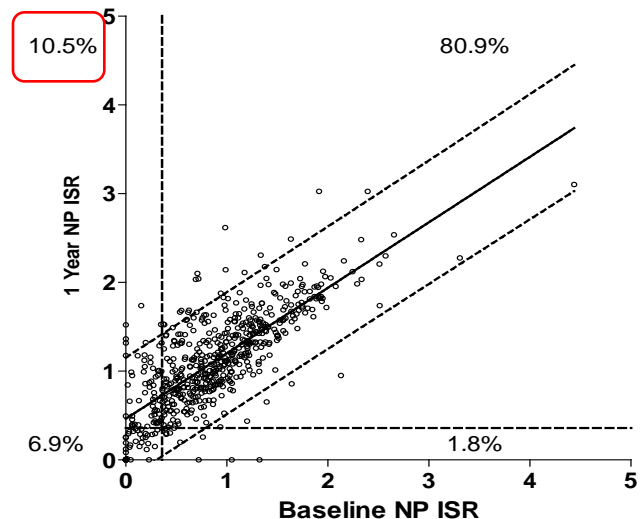
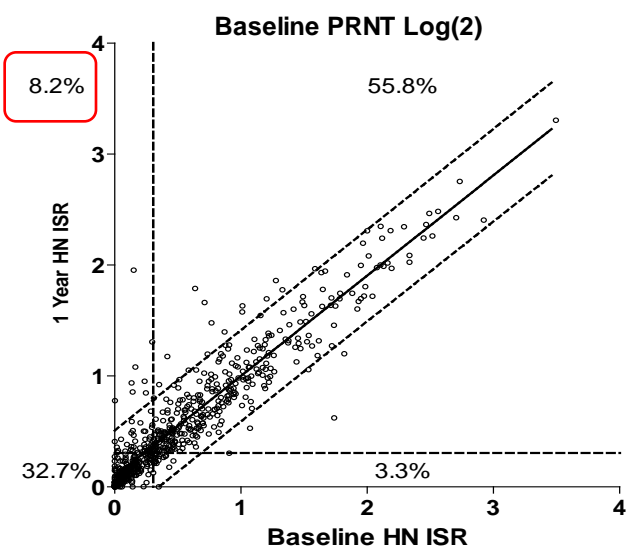
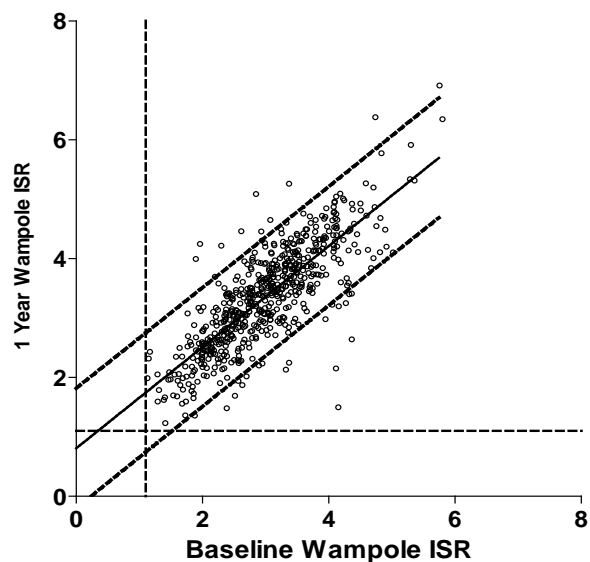
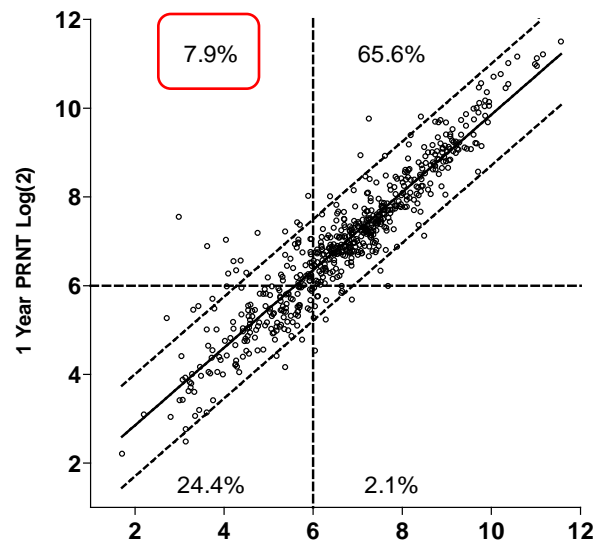
For more information, contact CDC
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Baseline vs. 1 Year Post-MMR3 Mumps Antibody Measurements: Individual Set Points with Modest Overall Increases



- Box indicates the proportion of subjects with low and negative antibody titers at baseline who had titers >low/negative 1 year post-MMR3
- The vertical and horizontal dotted lines represent cut-off for low/negative antibody titers

ISR=index standard ratio; NR=nucleoprotein; HN=hemagglutinin; PRNT=neutralizing antibody; Wampole –commercial whole virus assay; all assays used Jeryl Lynn vaccine virus as antigen. Unpublished data for HN and NP; Don Latner, PhD, [CDC] presentation to the WG, May, 2017 26

Orange County, NY - 3rd MMR Dose Study

Schools

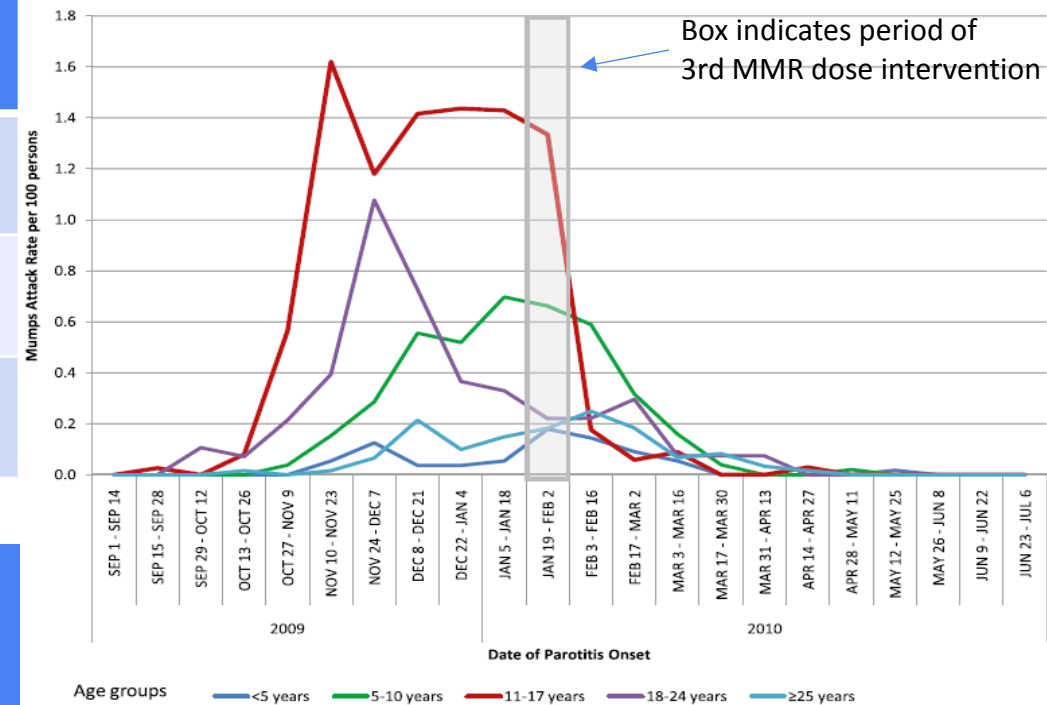
Schools	21 days Prevac	1st 21 days Postvax-P1	2 nd 21 days Postvax-P2	Relative Risk P2 vs. P1	Relative Risk 3- vs. 2-doses
All 6-12 gr students	113 (4.93)	35 (1.55)	3 (0.13)	0.06; p<.001	
2 MMR (n=420)		7 (1.67)	2 (0.48)	0.3 (0.06-1.40); P=.18	
3 MMR (n=1,751)		28 (1.60)	1 (0.06)	0.04 (0.005-0.27); p<.001	0.12 (0.01-1.32); p=.097

Community

Age group	21 days Prevac Cases (Attack rate)	1st 21 days Postvax-P1 Cases (Attack rate)	2 nd 21 days Postvax-P2 Cases (Attack rate)	Relative % Decline (95% CI)
All	172 (0.86)	87 (0.44)	41 (0.21)	76 (66, 83)
<5	7 (0.15)	11 (0.24)	5 (0.11)	27 (-126, 77)
5-10	60 (1.40)	40 (0.95)	16 (0.38)	73* (52, 84)
11-17	78 (2.40)	8 (0.26)	3 (0.10)	96* (87, 99)
18-24	17 (0.72)	7 (0.30)	8 (0.34)	53 (-11, 79)
≥25	10 (0.18)	21 (0.38)	9 (0.16)	11 (-123, 63)

* Decline statistically significant

Community, all age groups



Guam - 3rd MMR Dose Study

	>1 Incubation Period After 3 rd Dose Cases (Attack Rate)	Attack Rate 3- vs. 2-dose
≤2 MMR* (n=2,171)	5 (2.3)	
3 MMR (n=1,068)	1 (0.9)	0.4 (0.05-3.5); p=.67

*2-dose MMR coverage 99%-100%

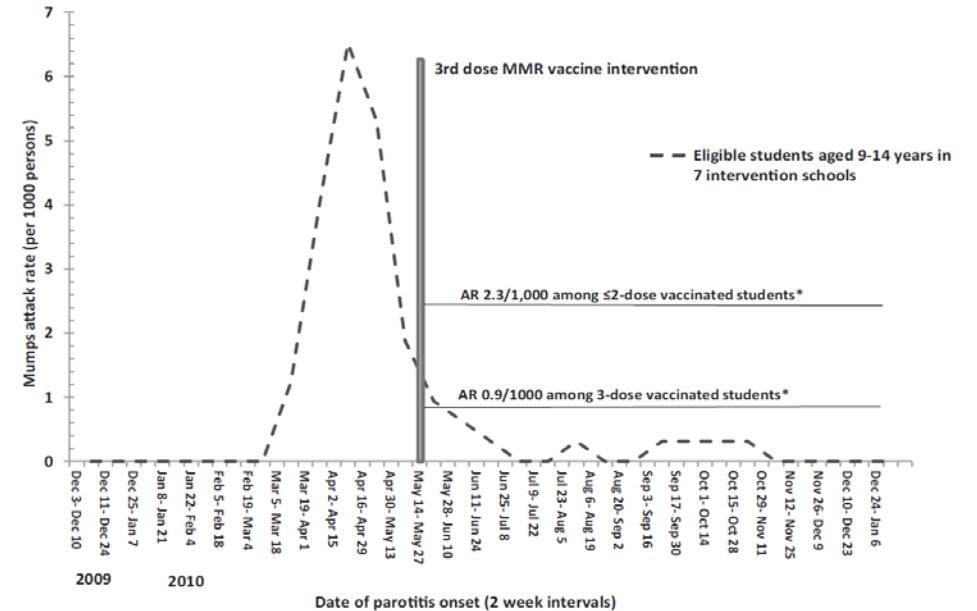


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