



Current Mumps Vaccination Recommendations and Epidemiology in the United States

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Outline

- Overview: mumps disease and transmission
- Mumps vaccine and vaccination recommendations in the United States
- Mumps epidemiology in the United States
- Topics for Work Group discussion

Mumps Disease

- Acute, viral illness that classically presents with parotitis (60%-70%)
- Other presentations
 - Other salivary gland swelling (10%)
 - Non-specific respiratory symptoms/asymptomatic infection (30%)

Complications	Unvaccinated (%)*	Vaccine era (%)†
Orchitis‡	up to 30%	3-11
Mastitis‡	up to 30%	≤1
Hearing loss	4	≤1
Pancreatitis	4	≤0.1
Aseptic meningitis	1-15	0.2-0.5
Encephalitis	0.03-0.5	0-0.3
Hospitalizations	5.5	<1-2

*McLean HQ et al. *MMWR* 2013; †Data from US outbreak investigations 2006-2015; ‡Assessed in postpubertal male/female patients

Mumps Transmission

- Person-to-person direct contact with infected droplets or saliva or by inhalation of infectious respiratory droplets
- Requires close contact for spread
 - Infectiousness is less than measles and varicella¹
- Infectious period: 2 days before to 5 days after parotitis onset
- Can occur from persons with non-specific respiratory symptoms and asymptomatic infection
- Incubation period: 16-18 days (range 12-25 days)
- Infectiousness before symptoms, transmission from persons with asymptomatic/non-specific presentation contribute to prolongation of transmission/outbreaks

¹Hope Simpson RE. *The Lancet* 1952 (secondary attack rate in households among those age <15 years: measles-76%, varicella-61%, mumps 31%)

Mumps Vaccine in the United States

- Single antigen vaccine licensed in 1967
- Currently available as combination vaccines (Merck & Co., Inc.)
 - Measles, mumps, rubella (MMR) licensed in 1971
 - Measles, mumps, rubella, varicella (MMRV) licensed in 2005
- Composition
 - Live, attenuated mumps strain
 - Jeryl Lynn strain, Genotype A
- Effectiveness estimates (MMR)¹
 - 1 dose: ~77% (49%-91%)²
 - 2 doses: ~88% (66%-95%)²

¹ Schaffzin JK et al. *Pediatrics* 2007, Marin M et al. *Vaccine* 2008, Cohen C et al. *Emerg Infect Dis* 2007, Deeks SL et al. *CMAJ*. 2011, Dominguez A et al. *Vaccine* 2010, Sartorius B et al. *Euro Surveill* 2005, Harling R et al. *Vaccine* 2005

²Ranges indicate results of individual studies and not confidence intervals

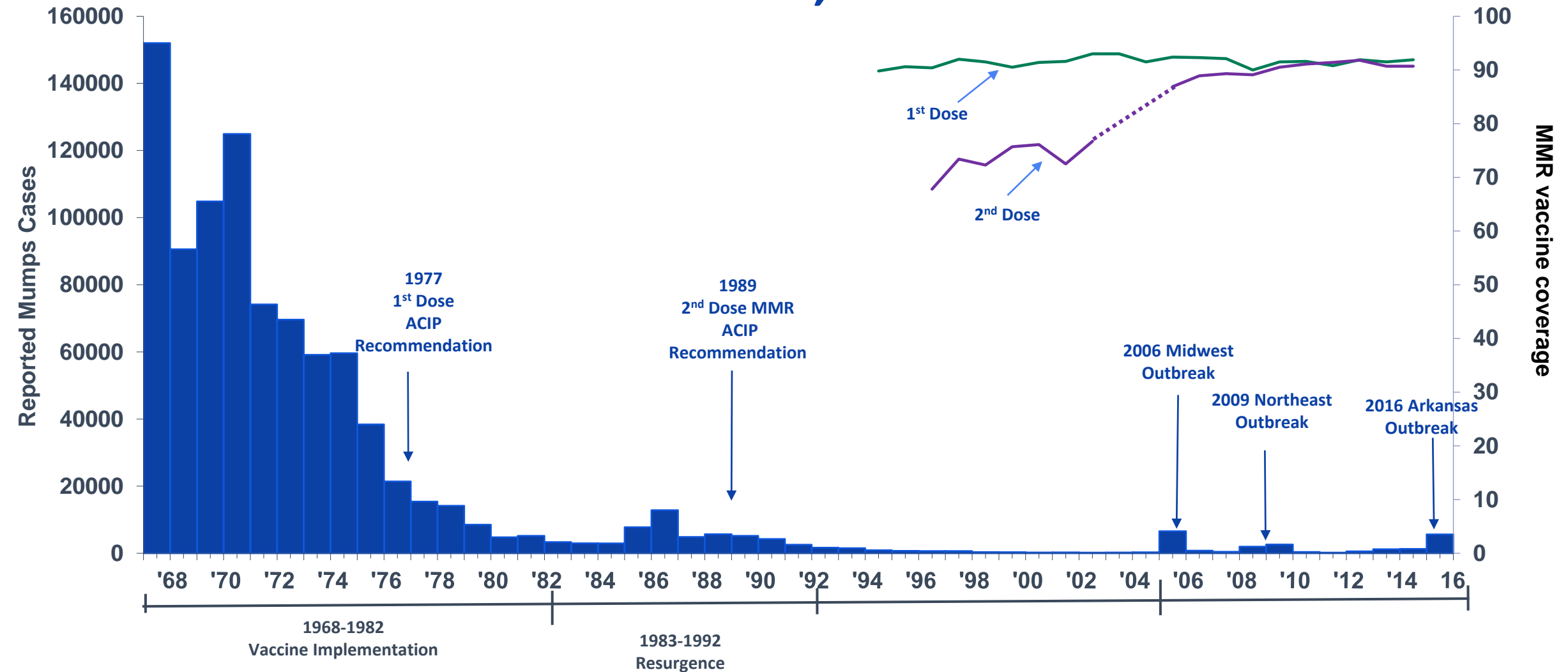
Mumps Vaccination Recommendations in the United States

- 1977*: 1 dose recommended for all children at any age after 12 months¹
- 1989: a second dose of *measles* vaccine recommended for improved measles control²
 - Both doses of measles vaccine should be given as combined MMR, stating that “mumps revaccination is particularly important”
 - Effectively, this delivered a second dose of mumps vaccine
- 2006: formal recommendation for 2 doses of a live mumps virus-containing vaccine³
 - School-aged children (grades K-12)
 - Adults in high risk groups
 - Healthcare facility personnel
 - International travelers
 - Students at post-high school educational institutions

Prior to 1977, mumps vaccine was not recommended for routine use: “may be considered for use in children approaching puberty, adolescents and adults, especially males” (1967), “may be used at any age from 12 months”, “vaccine is of particular value in children approaching puberty, adolescents and adults, especially males” (1968, 1972).

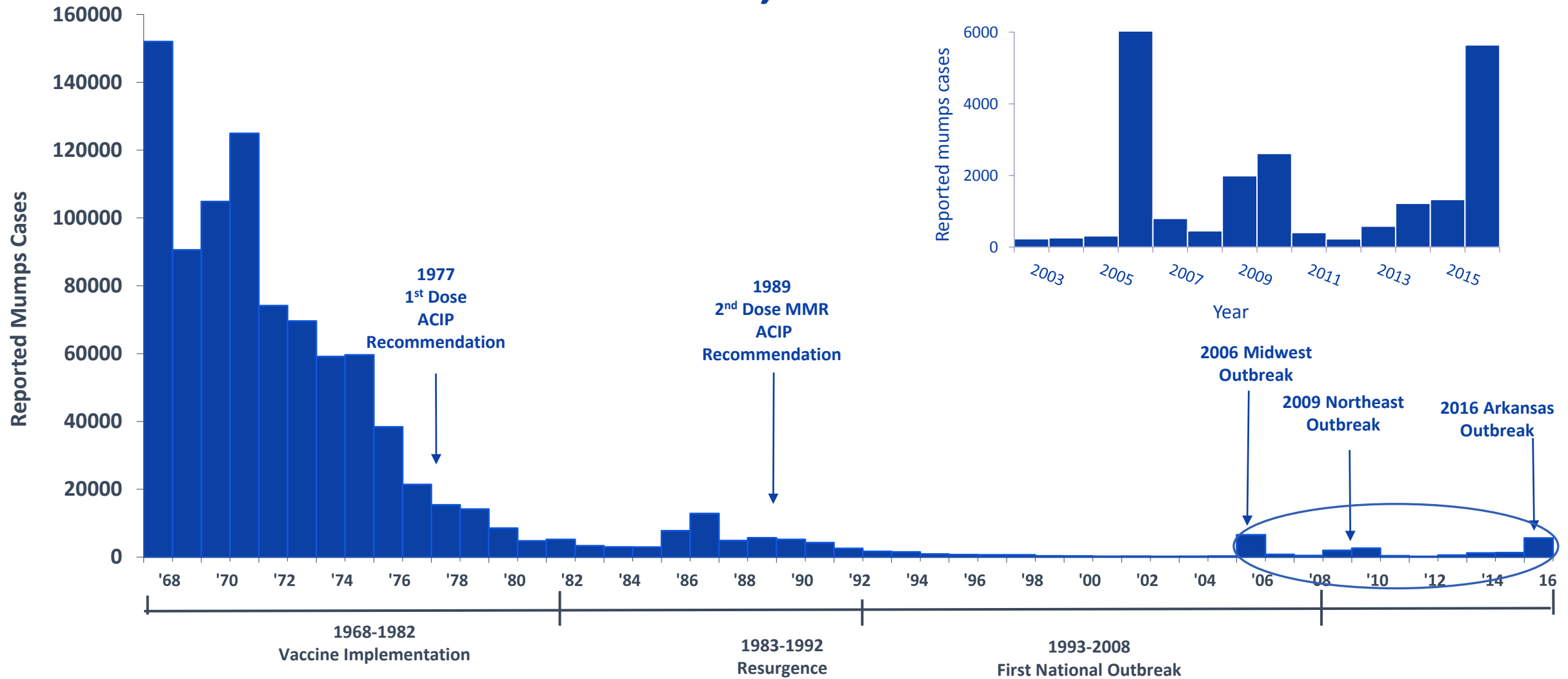
¹ACIP. *MMWR* 1977; 26:393-4; ²ACIP. *MMWR* 1989; 38(S-9):1-18; ³ACIP. *MMWR* 2006; 55(22):629-30

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



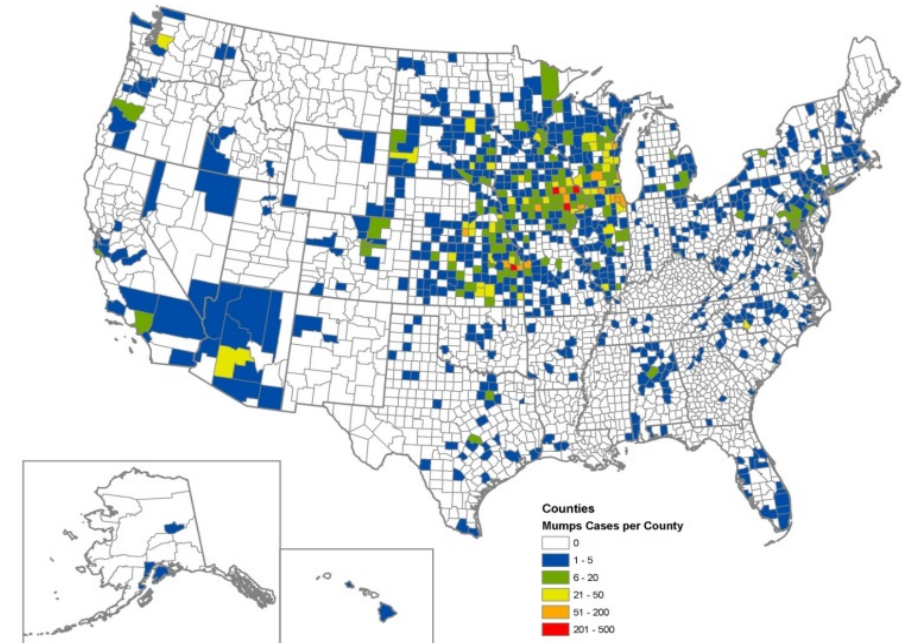
Source: National Notifiable Diseases Surveillance System (cases, passive surveillance); National Immunization Survey (NIS) (1st dose coverage 19-35 year olds), National Health Interview Survey & NIS-Teen (2nd dose coverage); 2016 case data is preliminary (Feb 9, 2017) and subject to change

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



Midwest Outbreak - 2006

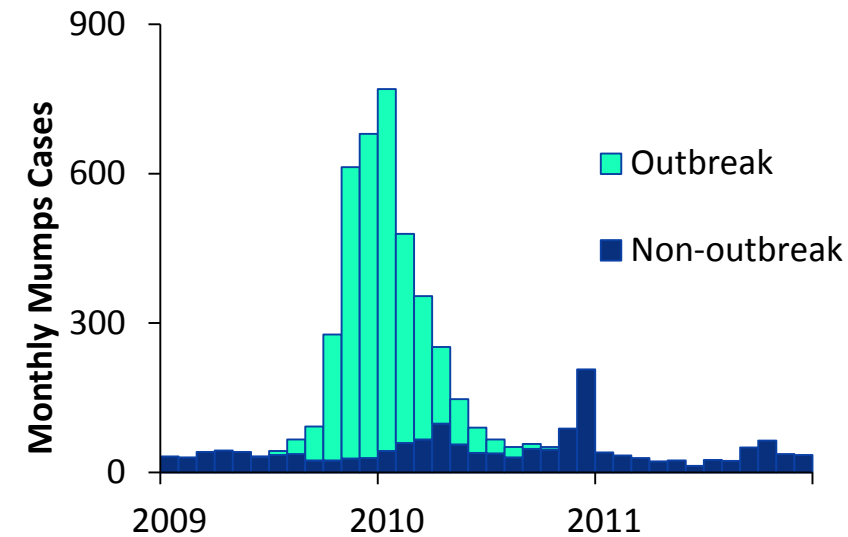
- 6,584 cases, geographically focused (85% in Midwest)
- First large outbreak attributable to 2-dose vaccine-failure
- Incidence was highest among young adults aged 18-24 years
 - Most were college students
 - 2 dose MMR coverage in affected colleges: 90%-99%
 - Most had received the second dose >10 years previously
 - Dormitory living, freshman class status, time since 2nd dose (≥10 years) were risk factors
- Standard control measures (e.g., isolation and vaccine catch-up campaigns) were implemented



Outbreaks in Northeast U.S. & Guam - 2009-2010

- Northeast: 3,502 cases¹
 - 97% of cases in Orthodox Jewish community
 - Adolescent (age 13-17 years) males the most affected group
 - 89% had 2 doses of MMR vaccine
 - Unique schools and large households; prolonged, intense exposures likely overcame protection afforded by the vaccine
- Guam: 505 cases²
 - Highest attack rate
 - School-aged children (aged 9-14 years), 96% two-dose vaccinated
 - Ethnic minorities with higher household densities
- 3rd MMR vaccine dose was used for outbreak control

Reported Mumps Cases, US, 2009-2011

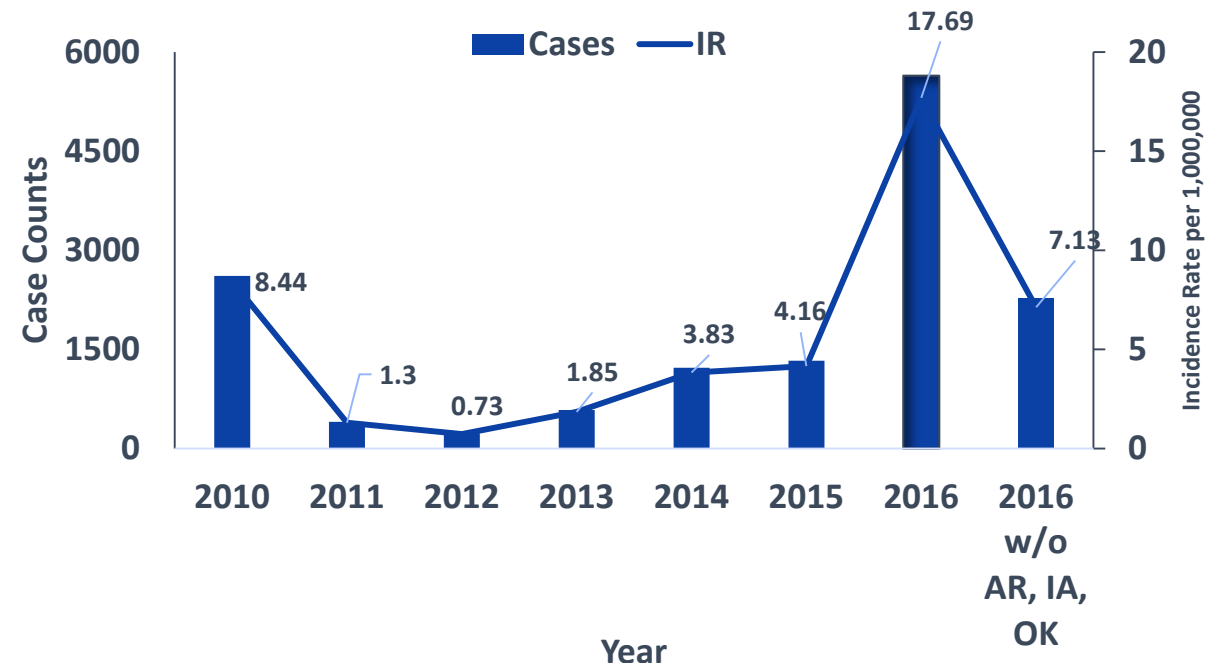


¹Barskey AE et al. *N Engl J Med* 2012; ²Nelson GE et al. *Pediatr Infect Dis J* 2013

Mumps Cases and Outbreaks, United States, July 2010-December 2016

- Increase in the number of reported cases and outbreaks
 - Genotype G virus
- 2010 through 2015: 23 outbreaks with ≥ 20 cases reported in 18 states
 - 22 (96%) occurred in close contact settings (18 in universities)
 - Highest incidence in the 18-25 years age group
 - Median age 19-23 years in 16 outbreaks
 - In half of university outbreaks $>85\%$ of case-patients had documented 2 MMR doses
 - Spread outside affected setting was minimal (3)

Mumps Cases and Incidence Rates by Year, 2010-Nov 2016



Source: National Notifiable Diseases Surveillance System (cases, passive surveillance); 2016 data is preliminary (Feb 9, 2017) and subject to change; Clemmons N, CDC, personal communication Feb 2017 (outbreaks)

Factors that May Contribute to the Increasing Number of Mumps Outbreaks (1)

- Vaccine effectiveness
 - 1 dose: ~77% (49%-91%)
 - 2 doses: ~88% (66%-95%)
- Waning of vaccine-induced immunity
 - Serologic studies suggest waning: seropositivity and neutralizing antibody titers decline over time¹⁻⁵,
 - No established correlates of protection, implications of declining titer uncertain³
 - Cellular immunity declines less than seropositivity over time (if at all)⁶
 - Epidemiologic studies suggest waning: decreased vaccine effectiveness⁷ and increased odds of disease with time since vaccination^{8,9}, evidence still limited
 - Waning of immunity does not explain the general geographical focal nature and that the oldest vaccinated cohorts not always most affected

¹Davidkin I et al. *J Infect Dis* 2008; ²LeBaron CW et al. *J Infect Dis* 2009; ³Rubin SA et al. *J Infect Dis* 2008; ⁴Date AA et al. *J Infect Dis* 2008;

⁵Kontio, *J Infect Dis* 2012; ⁶Jokinen S et al. *J Infect Dis* 2007; ⁷Cohen C et al. *Emerg Infect Dis* 2007; ⁸Cortese MM et al. *Clin Infect Dis* 2008;

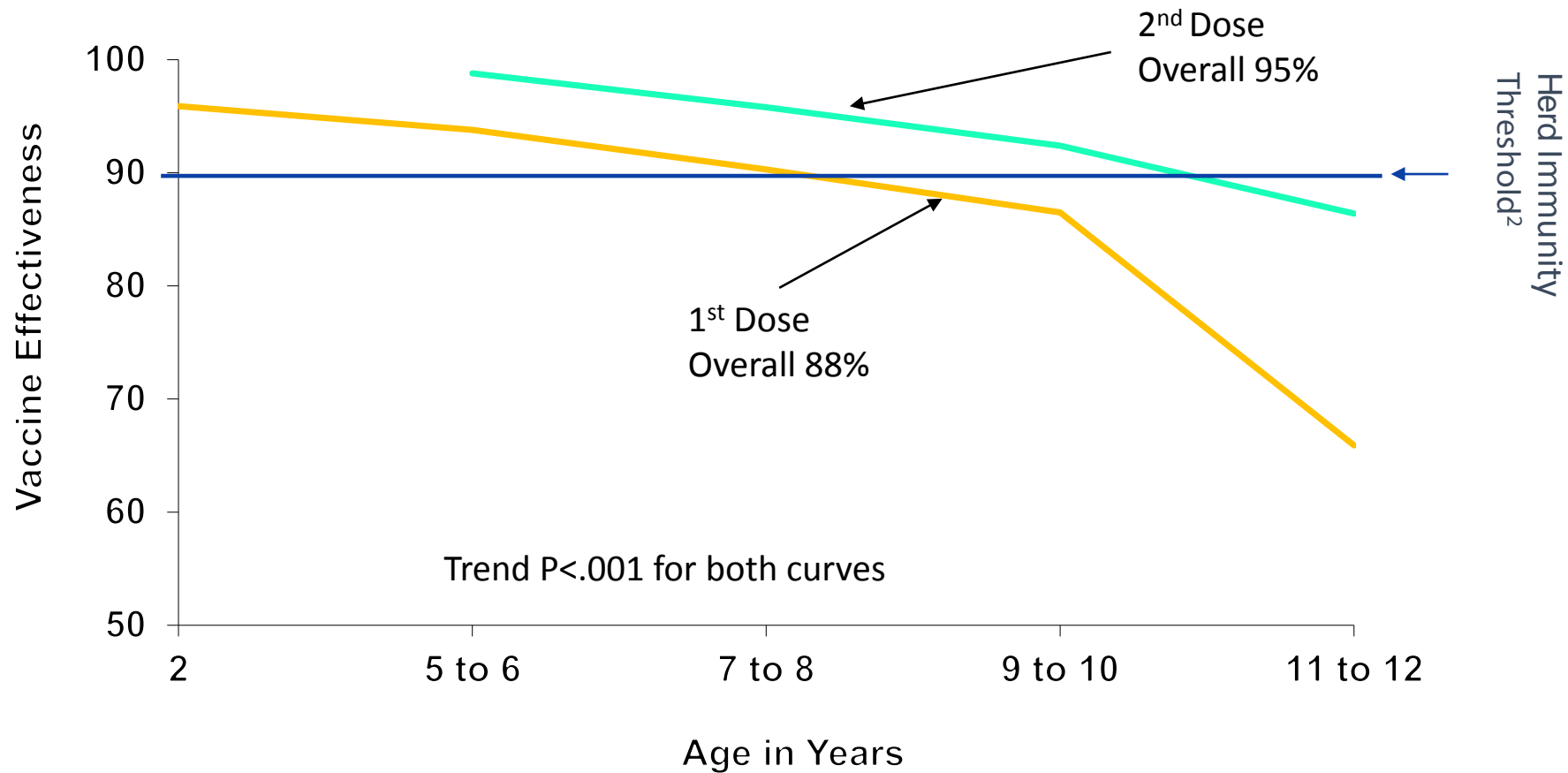
⁹Vygen S et al. *Euro Surveill* 2016

Factors that May Contribute to the Increasing Number of Mumps Outbreaks (2)

- Force of infection
 - Outbreaks in settings with high population density and contact rates that facilitate transmission (e.g., college campuses, close knit communities)
- Vaccine-induced immunity less effective against other strains?
 - No evidence to date, sera from vaccinated children neutralized diverse mumps strains^{1,2}
 - Antigenic differences among mumps virus strains detected¹⁻³
 - Lower antibody levels against non-vaccine strains
 - Might become more important with increasing time since vaccination

¹Rubin SA et al. *J Infect Dis* 2008; ²Rubin SA et al. *J Virol* 2012; ³Orvell C et al. *J Gen Virol* 2002

Age-specific Vaccine Effectiveness Estimates¹ for 1 and 2 Doses of MMR Vaccine*, UK, 2004-2005 Outbreak



¹Cohen C et al. *Emerg Infect Dis* 2007; ²Anderson RM, May RM. *Nature* 1985

*MMR vaccine contains either Jeryl Lynn strain or RIT 4385 strain (derived from the Jeryl Lynn strain)

Levels and Trend over Time of Vaccine-Induced Neutralizing Antibody

Table 1. Geometric mean titers (GMTs) of serum neutralizing antibody against the Jeryl Lynn and USA06-Iowa-G viruses.

Virus	2-5 years after MMR1	1 month after MMR2	10 years after MMR2
Jeryl Lynn	107.9 (83.6–139.2)	280.5 (212.1–371.0)	94.8 (73.2–122.9)
USA06-Iowa-G	56.2 (46.8–67.6)	110.4 (90.3–135.0)	56.6 (47.3–67.5)

NOTE. Data are the GMT (95% confidence interval). Titers were measured before administration of 2 doses of the measles, mumps, and rubella (MMR) vaccine (MMR2) (given 2–5 years after administration of 1 dose of the MMR vaccine [MMR1]) and at 1 month and 10 years thereafter.

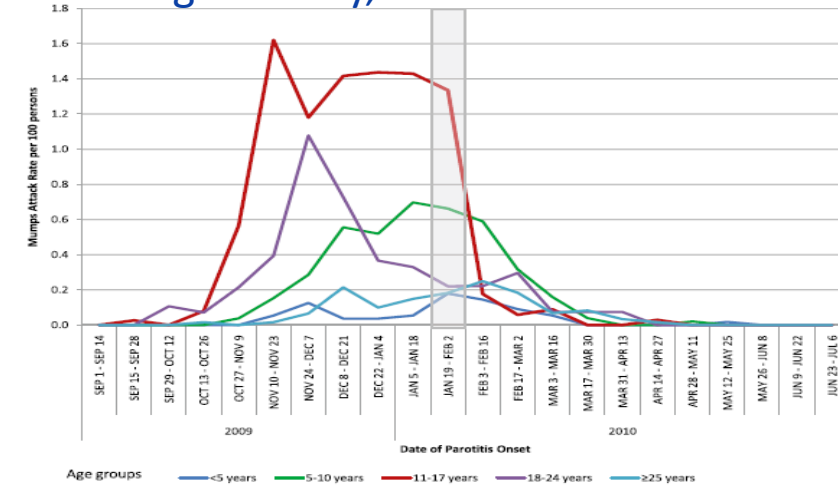
- Antibody induced by vaccination effectively neutralized genotype G virus, for all study subjects at each time point tested
- Geometric mean titers to genotype G strain were lower than those to Jeryl Lynn
- Antibody titers decreased over time
- Clinical significance of the findings cannot be conclusively ascertained

A 3rd Dose of MMR Vaccine in Northeast & Guam

Outbreaks, 2009-2010

- Northeast/Orange County, New York: 81% of eligible students vaccinated with a 3rd dose¹
- Guam: 33% of eligible students vaccinated with a 3rd dose²
- Attack rates declined after the 3rd MMR dose in both school-based studies, but
 - In Guam, statistical significance could not be established due to the small number of cases recorded
 - In both studies, late timing of 3rd dose campaigns
 - The possibility of the declines being unrelated to the intervention could not be excluded

Orange County, New York



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

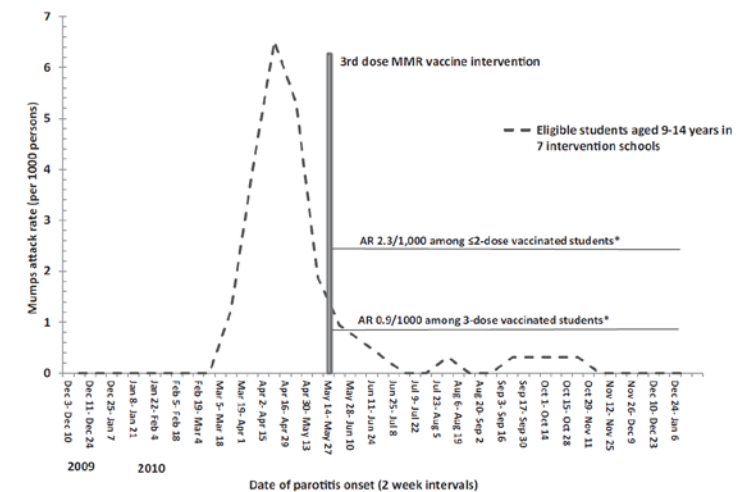


FIGURE 4. Comparison of mumps attack rates (cases/1000) postintervention among eligible students who received the third MMR vaccine dose compared with those who did not receive the third dose, Guam, December 1, 2009, to December 31, 2010. *More than 1 incubation period postintervention.

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

ACIP Statement Regarding a 3rd MMR Dose

- 2012: Data are *insufficient to recommend for or against* the use of a 3rd dose of MMR vaccine for mumps outbreak control
 - CDC issued guidance for consideration for use of a 3rd dose in specifically identified target populations along with criteria for public health departments to consider for decision making
 - Settings with >90% 2-dose vaccination coverage
 - Intense exposure settings such as schools and correctional facilities, and high attack rates (>5 per 1,000)
 - Ongoing transmission (>2 weeks)

Mumps Neutralizing Antibody in Young Adults After a 3rd Dose of MMR

- Very few subjects had titers negative (0.8%) or low (5.8%) before the 3rd dose
- Compared with pre-3rd dose (baseline), geometric mean titers were modestly but significantly higher one month and one year after the 3rd MMR dose
 - 104.1 (baseline) vs 159.2 (1 month); (P<0.0001)
 - 104.1 (baseline) vs 125.9 (1 year); (P<0.01)
- Minimal shifts in mumps titers from baseline to 1 month and 1 year

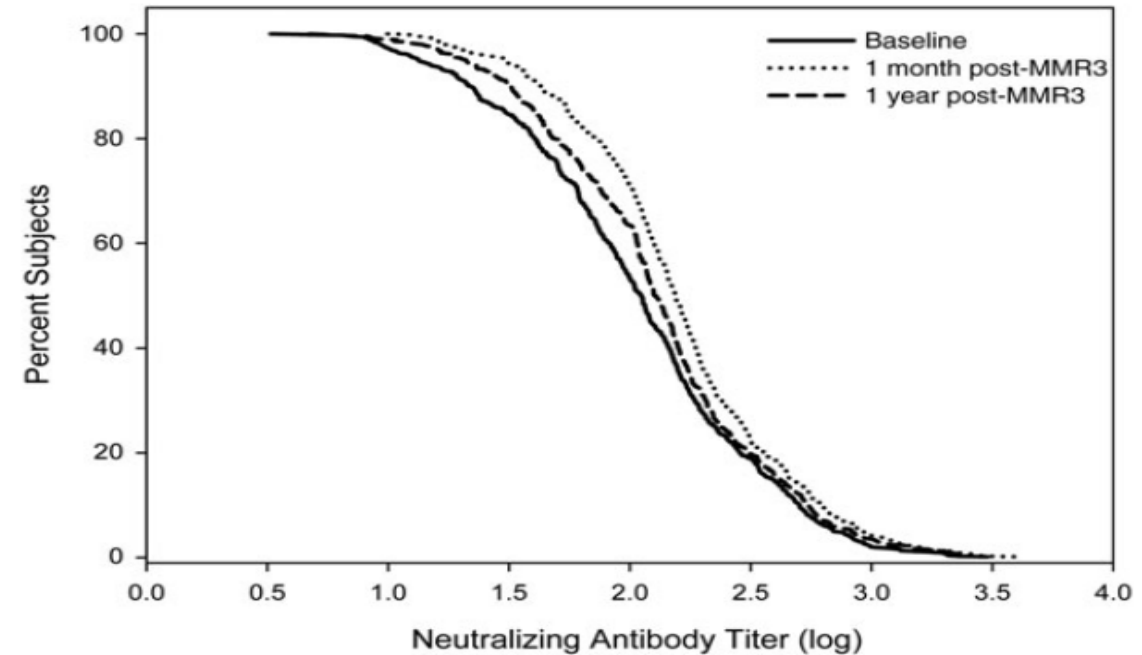


Figure 3. Reverse cumulative distribution curve using log-transformed titers by percent of subjects who had neutralizing mumps antibody titers at baseline and 1 month and 1 year following a third dose of measles-mumps-rubella (MMR3) vaccine.

Summary

- Use of the mumps vaccine reduced disease levels ~99% versus pre-vaccine era in the United States
- Since 2006, mumps outbreaks have occurred in highly 2-dose vaccinated populations
- Current 2-dose schedule is sufficient for mumps control in the general population, but outbreaks can occur in well vaccinated populations in specific settings
- Intense exposure settings and waning immunity appear to be risk factors for secondary vaccine failure
- The benefit of a 3rd MMR dose still needs to be assessed

Topics for Work Group Discussion

- Review available evidence for risk factors for mumps among 2 dose MMR vaccine recipients
 - Protection against currently circulating mumps virus genotypes in the United States
- Review available evidence on benefit provided by the 3rd MMR dose
 - Additional benefit?
 - Short vs. long term
 - More epidemiologic and laboratory data forthcoming
- Policy options for prevention and control of mumps outbreaks in the United States
 - Programmatic implications and cost analysis of various policy options for a 3rd dose MMR to prevent or control mumps outbreaks

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