



# **Considerations for the Use of the 3<sup>rd</sup> Dose of MMR Vaccine For Persons at Increased Risk Because of a Mumps Outbreak and Proposed Recommendations**

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# Context

- Numerous mumps outbreaks reported since late 2015, with majority occurring in university settings
  - Young adults at highest risk
- CDC guidance for health departments for use of a 3<sup>rd</sup> dose of MMR (MMR3) vaccine in outbreak settings available since 2012
  - Data insufficient to recommend for or against MMR3 during mumps outbreaks
  - ACIP recommendation would provide a more direct recommendation to stakeholders
- Evidence limited and insufficient at this time to fully characterize impact of MMR3 on reducing size or duration of mumps outbreaks
  - Studies ongoing
- Evidence available for a potential recommendation to decrease risk for mumps disease in persons at increased risk because of an outbreak

# GRADE Process

## Policy Question: Should a 3<sup>rd</sup> Dose of MMR Vaccine Be Administered to Persons at Increased Risk for Mumps Because of an Outbreak?

- Develop policy questions
- Consider critical outcomes
- Review and summarize evidence of benefits and harms
- Evaluate quality of evidence
- Assess population benefit
- Evaluate values and preferences
- Review health economic data
- Considerations for formulating recommendations
- Work Group (WG) proposed recommendation and GRADE category



GRADE presentation\*

# Outline: Review of the Evidence

- Evidence reviewed by WG
  - Summary of evidence
  - WG interpretation of evidence
- Used *Draft* ACIP Evidence to Recommendation Framework

Evidence/Factor	Question
<b>Problem</b>	<ul style="list-style-type: none"><li>• What is the public health priority for the mumps program?</li></ul>
<b>Benefits and harms</b>	<ul style="list-style-type: none"><li>• Do the desirable effects outweigh the undesirable effects?</li><li>• What is the certainty of the evidence for the critical outcomes?</li></ul>
<b>Values</b>	<ul style="list-style-type: none"><li>• How does the target population view the balance of desirable vs. undesirable effects?</li></ul>
<b>Acceptability</b>	<ul style="list-style-type: none"><li>• Is the option acceptable to the key stakeholders?</li></ul>
<b>Implementation</b>	<ul style="list-style-type: none"><li>• Is the option feasible to implement?</li></ul>

# Problem

# Problem

## ■ Summary of evidence

- Two-dose MMR childhood vaccination program led to significant decline in reported mumps cases in the United States
  - Mumps can occur in persons vaccinated with 2 doses of MMR (MMR2); incidence significantly lower in the 2-dose era compared with prevaccine and 1 dose eras
- Increase in the number of cases and outbreaks since 2006
  - Outbreaks reported in settings with high MMR2 coverage
    - › Most in populations with high contact rates that facilitate transmission, mainly universities
- Mumps outbreaks occurring in more US jurisdictions in recent years
- Outbreak control measures are resource-intensive for institutions and public health
- Severity of mumps among MMR2 vaccinated persons is reduced

## ■ WG interpretation of evidence

- Outbreaks (vs. sporadic disease) are a public health priority for the mumps vaccination program

# 2-dose MMR Vaccine Effectiveness for Prevention of Mumps

## ■ Summary of evidence

- Median 2-dose mumps vaccine effectiveness is 88% (20 estimates, range: 31%-95%)
  - Most studies included persons with MMR2 receipt <10 years prior
  - 7 studies among young adults: median: 84% (31%-89%)
- Increased risk for mumps<sup>1</sup> and decreased vaccine effectiveness with longer time since MMR2<sup>2</sup>
- Risk for mumps complications lower among MMR2 vaccinated case-patients vs. unvaccinated<sup>3</sup>
- Outbreaks occurred in residential or educational settings with high population density; spread to the broader community limited

## ■ WG interpretation of evidence

- The 2-dose program is acceptably effective at preventing mumps disease and complications in the general population
- The 2-dose program is not sufficiently effective at preventing mumps outbreaks in all close contact settings; however, protection against severe disease is maintained

# Immune Response to Wild-type and Vaccine Mumps Virus

- Summary of evidence
  - Based on limited laboratory data, compared with measles and rubella
    - Lower antibody levels after mumps natural infection or vaccination<sup>1</sup>
    - Lower quality antibodies: avidity, fewer memory B cells/failure to generate a strong memory B cell response<sup>2</sup>
  - Neutralizing antibodies important for protection, persons with lower neutralization titer had increased risk for disease; no defined immunologic correlate of protection<sup>3</sup>
  - Mean mumps antibody titers (both neutralizing and non neutralizing) decline over time in MMR2 vaccine recipients<sup>4</sup>
- WG interpretation of evidence
  - Immune response to mumps virus is less robust compared with response to measles and rubella viruses
  - Vaccine-induced mumps virus-specific antibodies wane over time potentially leading to inadequate protection against mumps for populations in conditions of highest risk

1. Lerman et al. *Pediatrics* 1981; Gans et al. *J Infect Dis* 2001; 2. Kontio et al. *J Infect Dis* 2012; Latner et al. *Clin Vaccine Immunol* 2011;  
3. Cortese et al. *J Infect Dis* 2011; Gouma et al. *Open Forum Infect Dis* 2014; 4. Davidkin et al. *J Infect Dis* 2008; LeBaron et al. *J Infect Dis* 2009;  
Rubin et al. *J Infect Dis* 2008; Date et al. *J Infect Dis* 2008; Kontio et al. *J Infect Dis* 2012



# Changes in Molecular Epidemiology of Wild-type Mumps Virus

- Summary of evidence
  - Vaccine contains genotype A virus; since 2006, genotype G predominantly circulating in the US
  - No evidence to date that circulating mumps strains escape vaccine-induced immunity
    - MMR2 vaccine recipients all had neutralizing antibody\* against genetically diverse mumps strains when studied soon and 10 years after vaccination<sup>1</sup>
  - Lower (~one-half) neutralizing antibody geometric mean titers to non-vaccine strains compared to Jeryl Lynn vaccine strain in MMR2 vaccine recipients<sup>1</sup>
    - Significance is difficult to interpret in the absence of a known level of neutralizing antibody that predicts protection
- WG interpretation of evidence
  - There is insufficient evidence to support that antigenic differences between vaccine and circulating mumps strains are a major contributor to the current burden of mumps

\*Titer  $\geq 1:4$

1. Rubin et al. *J Infect Dis* 2008; Rubin et al. *J Virol* 2012

# Problem: Summary

Factor	Question	WG Interpretation
<b>Problem</b>	<ul style="list-style-type: none"><li>What is the public health priority for the mumps program?</li></ul>	<ul style="list-style-type: none"><li>Persons at increased risk for mumps because of an outbreak are a public health priority for the mumps vaccination program; waning immunity from vaccination in the setting of increased force of infection typical of outbreaks contributes to this risk</li></ul>

# Benefits and Harms of Intervention (MMR3)

# Policy Question: Should a 3<sup>rd</sup> Dose of MMR Vaccine Be Administered to Persons at Increased Risk for Mumps Because of an Outbreak?

<b>Population</b>	Persons at increased risk for mumps because of an outbreak	
<b>Intervention</b>	Third dose of MMR vaccine (MMR3)	
<b>Comparison</b>	Two doses of MMR vaccine (MMR2)	
<b>Outcomes</b>	Benefits <b>1. Prevention of mumps disease</b> <b>2. Prevention of complications of mumps disease</b> 3. Duration of protection 4. Immune response	Harms <b>1. Serious adverse events</b> 2. Reactogenicity

Bold font indicates outcomes considered by the WG “Critical” for GRADE analysis

# Benefits and Harms of MMR3

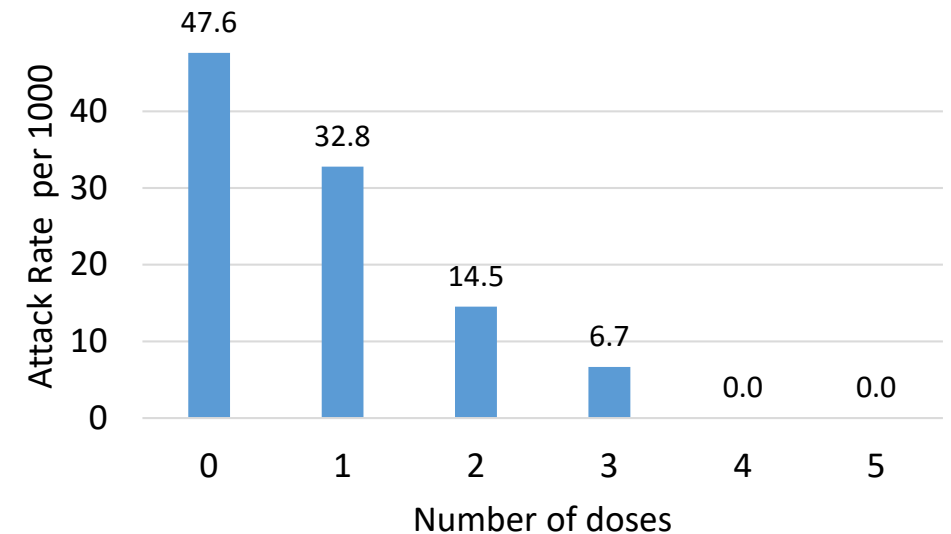
Benefits	Summary of evidence
<b>Prevention of mumps</b>	3 studies: lower attack rate in MMR3 vs. MMR2 vaccine recipients; vaccine effectiveness 61% to 88%, one estimate significant (78%)
<b>Prevention of mumps complications</b>	
Duration of protection	
Immune response	

Bold font indicates outcomes considered by the WG “Critical” for GRADE analysis

# University of Iowa Mumps Outbreak, 2015-2016

- Lower attack rate for mumps in students vaccinated with MMR3 vs. MMR2 ( $p < 0.001$ )
- Increase in the risk for mumps with increased time since MMR2
- Receipt of MMR3 associated with a 78%\* lower risk for mumps than receipt of MMR2 (95% confidence interval: 61%-88%)

Attack Rate by Dose Status



\*Postvaccination window of 28 days and after adjustment for the number of years since MMR2; vaccine effectiveness was 68% (95% confidence interval: 42%-83%) when cases prior to campaign were excluded

Cardemil et al. *N Engl J Med* 2017

# Benefits and Harms of MMR3

Benefits	Summary of evidence
<b>Prevention of mumps</b>	3 studies: lower attack rate in MMR3 vs. MMR2 vaccine recipients; vaccine effectiveness 61% to 88%, one estimate significant (78%)
<b>Prevention of mumps complications</b>	No clinical studies; by preventing disease in MMR3 vaccine recipients, complications also are prevented
Duration of protection	No clinical studies
Immune response	

Bold font indicates outcomes considered by the WG “Critical” for GRADE analysis

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<b>Prevention of mumps</b>	3 studies: lower attack rate in MMR3 vs. MMR2 vaccine recipients; vaccine effectiveness 61% to 88%, one estimate significant (78%)
<b>Prevention of mumps complications</b>	No clinical studies; by preventing disease in MMR3 vaccine recipients, complications also are prevented
Duration of protection	No clinical studies
Immune response	Increase in proportion of seropositive persons and antibody titers at 1 month post-MMR3; trend towards decline in proportion of seropositive persons and antibody titers at 12 months post-MMR3

Bold font indicates outcomes considered by the WG “Critical” for GRADE analysis



# Benefits and Harms of MMR3

Harms	Summary of evidence
<b>Serious adverse events</b>	No serious adverse events or vaccine-related health care visits in 14,368 MMR3 vaccine recipients
Reactogenicity	Overall, local and systemic non-serious adverse events post-MMR3 were mild and reported at low rates; among young adults, headache, joint pain, diarrhea and swollen glands reported at higher rates post MMR3 compared with pre-MMR3, short duration (median = 1-3 days)

Bold font indicates outcome considered by the WG “Critical” for GRADE analysis

# Balance of Benefits and Harms of MMR3: WG Interpretation

Factor	Question	WG Interpretation
<b>Benefits and harms</b>	<ul style="list-style-type: none"><li>• Do the desirable effects outweigh the undesirable effects?</li><li>• What is the certainty of the evidence for the critical outcomes?</li></ul>	<ul style="list-style-type: none"><li>• The benefits of MMR3 outweigh the risks</li><li>• Data demonstrate short-term benefit of MMR3 vaccine for persons in outbreak settings</li><li>• No concerns for serious adverse events after MMR3; injection site reactions and non-serious systemic adverse events were mild and reported at low rates</li><li>• Evidence type: 4 for benefits, 2 for harms</li></ul>

# Values, Acceptability, and Implementation

# Values, Acceptability, and Implementation

- Surveys of stakeholders

- Values

- Acceptability

- Implementation

Stakeholders

Students and parents\*

Health Departments  
and  
Universities/Colleges†

\*Low response rate in the university that agreed to participate; data not presented

† Will be referred to as Universities

# University Survey

- Survey distributed through the American College Health Association (ACHA)
- 26% (251/980) ACHA member student health service administrators responded
  - 47 states
  - 31% (79/251) had mumps cases on campus since August 2014
    - 41% (32/79) had a mumps outbreak
    - 22% (17/79) recommended an outbreak/MMR3 dose

Outbreak dose: an MMR dose was administered without checking individual records prior to vaccination.

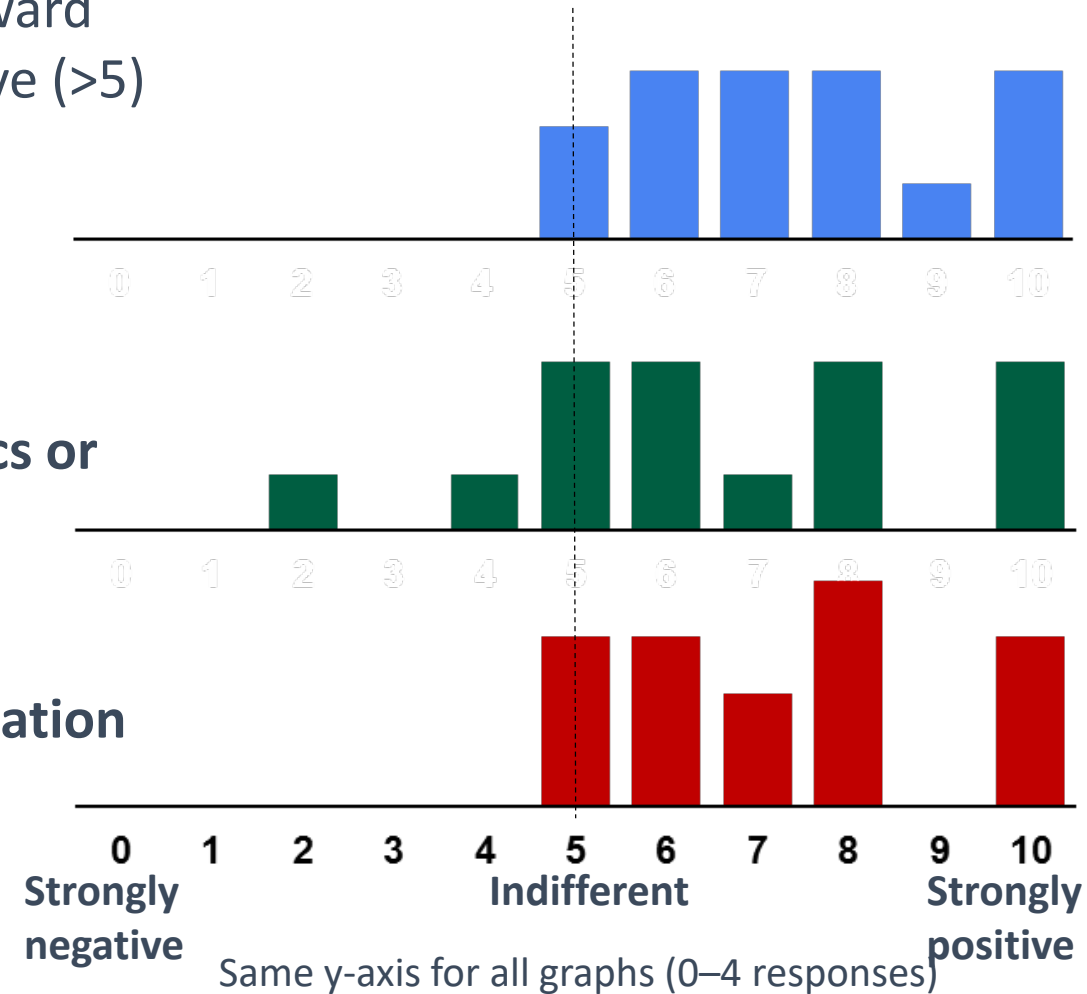
MMR3 dose: dose was administered after checking individual records and persons with documented 2 doses of MMR vaccine received a 3<sup>rd</sup> dose.

# University Survey

## Experience of Student and Parent Attitudes Toward Outbreak/MMR3 Dose (n=15\*)

Most respondents ranked student and parent attitudes toward MMR3 to protect the student during an outbreak as positive (>5)

- 83% ranked **students'** attitudes toward the **recommendation** as >5
  - Median=7
- 67% ranked **students'** attitudes toward **attending clinics or campaigns** as >5
  - Median=6
- 80% ranked **parents'** attitudes toward the **recommendation** as >5
  - Median=7

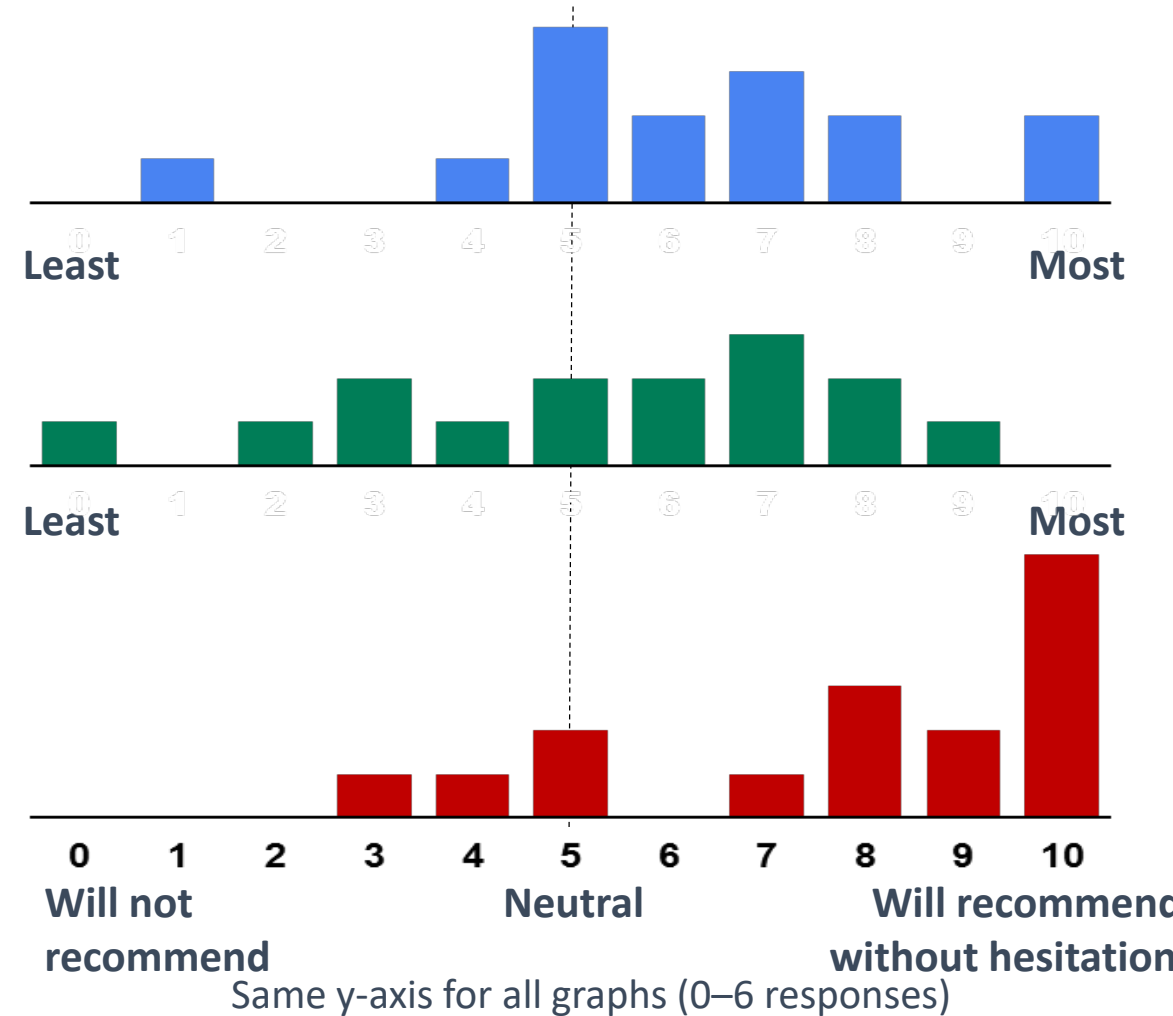


\*Colleges and universities that recommended an outbreak/MMR3 dose and answered the questions, 13 (76%) held special clinics/campaigns  
Marlow M. Mumps outbreak experiences and practices. Results from college and university survey. ACIP Mumps WG, September 2017

# University Survey

## Experience With Using an Outbreak/MMR3 Dose Recommendation (n=16\*)

- 60% gave outbreak/MMR3 an **effectiveness** score >5 (better than neutral)
  - Median=6
- 53% gave outbreak/MMR3 a **cost-benefit** score >5 (better than neutral)
  - Median=6
- 75% were **likely to recommend** outbreak/MMR3 dose again
  - 38% would recommend without hesitation
  - Median=8



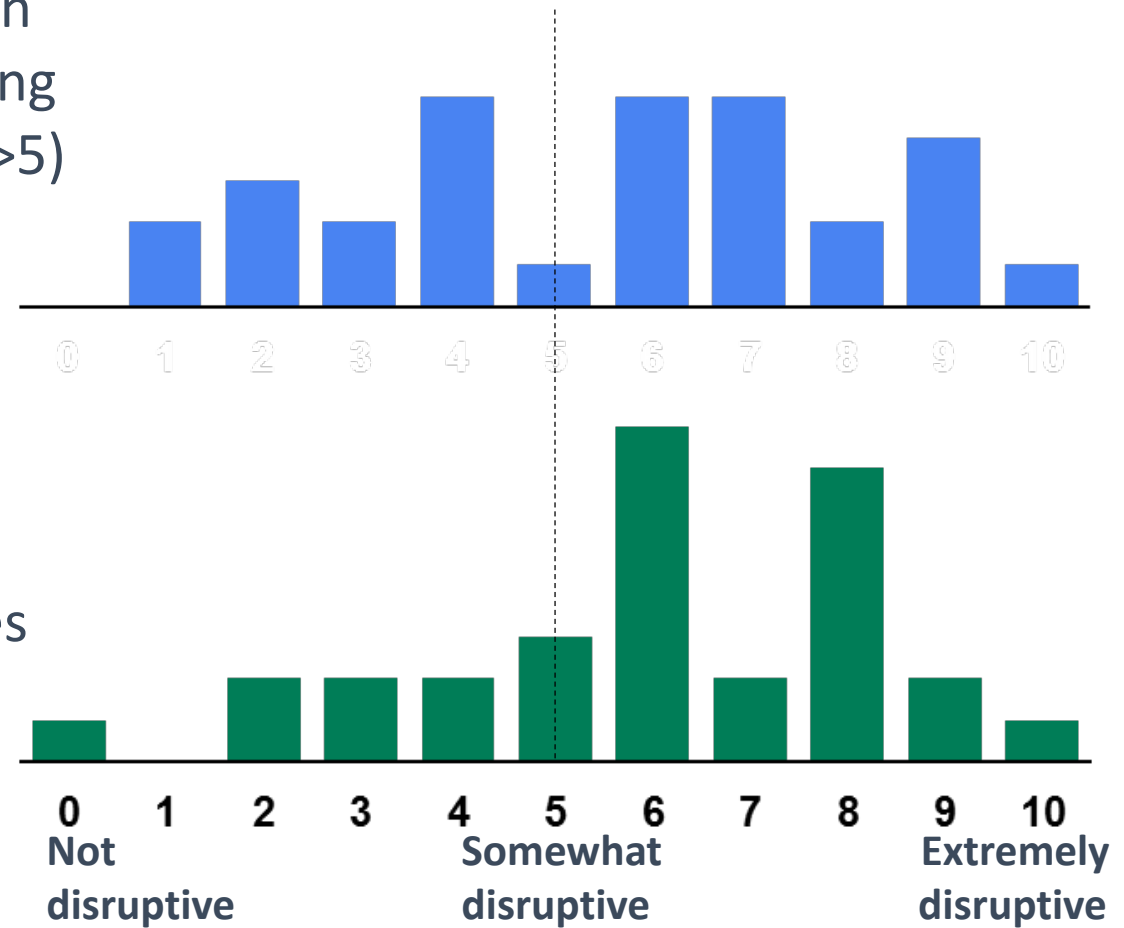
\*Colleges and universities that recommended an outbreak/MMR3 dose and answered the questions, 13 (76%) held special clinics/campaigns  
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# University Survey

## Disruption to Campus Activities Caused by Mumps Outbreaks (n=30\*)

Almost all respondents indicated outbreaks resulted in some degree of disruption on campus, with half placing the intensity of disruption in the upper half of scale (>5)

- 57% ranked disruption to **student life** as >5
  - Median=6
  
- 67% ranked disruption to **staff and admin** activities as >5
  - Median=6



Same y-axis for both graphs (0–8 responses)

Results did not differ by outbreak size

\*Colleges and universities that had outbreaks (19 with >10 cases, none with >500 cases) and answered the questions



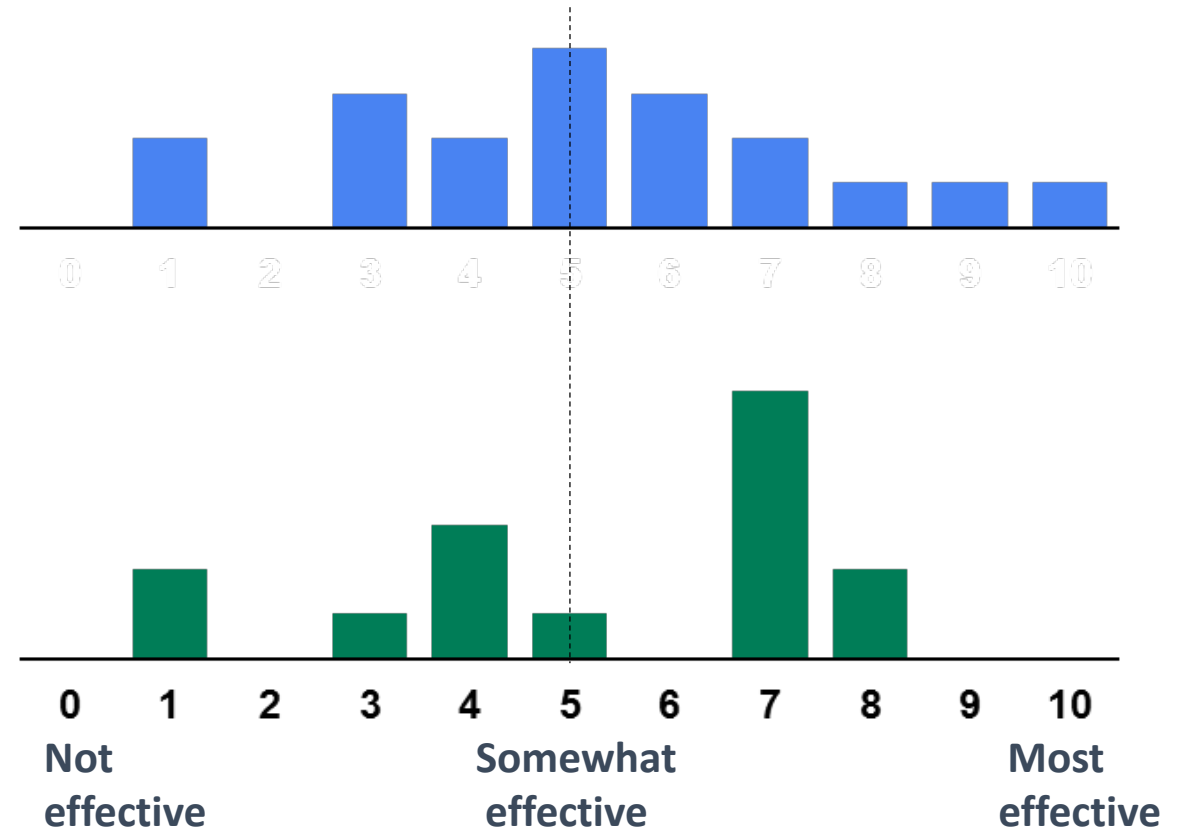
# Health Department Survey

- Survey distributed through Council of State and Territorial Epidemiologists to 62 state and territorial and 23 city/large urban health departments
- 72% (61/85) health department jurisdictions responded
  - 75% (46/61) reported having  $\geq 1$  mumps outbreak since Jan 1, 2016
    - 47% (20/43) reported recommending an outbreak/MMR3 dose during  $\geq 1$  outbreak

# Health Department Survey

## Experience With Using an Outbreak/MMR3 Dose Recommendation (n=20\*)

- 42% gave MMR3 an **effectiveness** score >5 (more than somewhat effective)
  - Median=5
  
- 53% gave MMR3 a **cost-benefit** score >5
  - Median=7



\*Same y-axis for both graphs (0-6 responses)

\*Health departments that recommended an outbreak/MMR3 dose

Marlow M. Mumps outbreak experiences and practices. Results from health department survey. ACIP Mumps WG, September 2017

# Values, Acceptability, Implementation: WG Interpretation

Factor	Question	WG Interpretation
<b>Values</b>	<ul style="list-style-type: none"> <li>How does the target population view the balance of desirable vs. undesirable effects?</li> </ul>	<p>Expert opinion:</p> <ul style="list-style-type: none"> <li>Students and parents are concerned about mumps complications and potential for loss of productivity</li> <li>Not concerned with serious adverse events</li> </ul>
<b>Acceptability</b>	<ul style="list-style-type: none"> <li>Is the option acceptable to the key stakeholders?</li> </ul>	<ul style="list-style-type: none"> <li>Stakeholders who implemented an outbreak/MMR3 recommendation had a positive experience overall, including a positive assessment of students' and parents' attitudes</li> </ul>
<b>Implementation</b>	<ul style="list-style-type: none"> <li>Is the option feasible to implement?</li> </ul>	<p>An ACIP recommendation would</p> <ul style="list-style-type: none"> <li>Allow health departments to make more rapid decisions regarding use of MMR3</li> <li>Increase access to MMR3 for persons identified at increased risk because of an outbreak</li> </ul> <p>Additional implementation guidance from CDC will be needed</p>

# CDC Guidance for Outbreak Control

- CDC will update guidance for use of MMR3 during mumps outbreaks with input from WG and other stakeholders
- Factors to be considered:
  - Size of target population
  - Mumps incidence/no. of cases
  - MMR3 vaccine coverage needed to impact the outbreak
  - Timing of MMR3 vaccination
  - Social networks
  - Intensity and duration of close contact

# Ongoing/Planned CDC Activities

- Develop transmission models to examine factors that impact size and duration of an outbreak
- Examine contribution of antigenic differences between vaccine and circulating mumps strains on burden of mumps
- Evaluate quality of antibodies (e.g., avidity) after MMR3 vs. MMR2
- Monitor burden of disease over time among MMR3 vaccine recipients to better characterize duration of enhanced protection after MMR3

# Conclusions – Overall Balance of Consequences

# Policy Question: Should a 3<sup>rd</sup> Dose of MMR Vaccine Be Administered to Persons at Increased Risk for Mumps Because of an Outbreak?

Factor	WG Interpretation
<b>Problem</b>	Persons at increased risk for mumps because of an outbreak are a public health priority for the mumps vaccination program; waning immunity in the setting of increased force of infection typical of outbreaks contributes to this risk
<b>Benefits and harms</b>	Benefits outweigh the risks; evidence type is 4 for effectiveness and 2 for safety
<b>Values</b>	WG considered that persons in outbreak settings value prevention of: mumps, mumps complications, and loss of productivity
<b>Acceptability</b>	MMR3 vaccination was considered acceptable to students, parents, universities/schools, and health departments
<b>Implementation</b>	Providers and the target population have experience with MMR vaccination. Public health should be involved in identifying target groups at increased risk for mumps
<b>Summary</b>	WG agreement that a 3 <sup>rd</sup> dose of MMR vaccine would improve protection for persons at increased risk for mumps because of an outbreak

# WG Deliberations Regarding Proposed Recommendation



# WG Deliberations Regarding Proposed Recommendation (1)

- Unanimity among WG members that there is sufficient evidence to propose a recommendation to decrease risk for mumps disease in persons at increased risk because of an outbreak
- WG considered that public health should have a role in designating/identifying groups at increased risk
  - Public health routinely involved in declaring and responding to outbreaks and determining groups at increased risk
  - Helpful for providers who are not directly associated with the outbreak setting

# WG Deliberations Regarding Proposed Recommendation (2)

- Majority of WG members favored
  - Persons previously vaccinated with two doses of MMR vaccine who are identified by public health as at increased risk for mumps because of an outbreak should receive a third dose of MMR vaccine to improve protection against mumps disease and related complications
- Small minority of WG members preferred
  - Persons previously vaccinated with two doses of MMR vaccine who are identified by public health as at increased risk for mumps because of an outbreak may receive a third dose of MMR vaccine to improve protection against mumps disease and related complications

# Proposed Recommendation vs. Existing Recommendations for Mumps Vaccination

Vaccination status	Existing recommendations to receive a dose (or 2) of MMR vaccine?*
Unvaccinated	Yes
1-dose vaccinated	
2-doses routinely recommended	Yes
1-dose routinely recommended	Yes, during outbreaks
2-dose vaccinated	No
3+-dose vaccinated	No†
Unknown vax status	Yes

\*McLean HQ et al. ACIP MMR vaccine recommendations. *MMWR* 2013

†Guidance will indicate: No additional dose is recommended for persons with documentation of three valid doses of MMR/a mumps-containing vaccine.

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- Jessica Leung
- ACIP Mumps Work Group
- CDC Mumps Team

# WG Proposed Recommendations

# Policy Question: Should a 3<sup>rd</sup> Dose of MMR Vaccine Be Administered to Persons at Increased Risk for Mumps Because of an Outbreak?

- Persons previously vaccinated with two doses of a mumps-containing vaccine\* who are identified by public health as at increased risk for mumps because of an outbreak should receive a third dose of a mumps-containing vaccine to improve protection against mumps disease and related complications

\*As stated in Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps, 2013:

Summary Recommendations of the Advisory Committee on Immunization Practices (ACIP); wording includes MMR and MMRV

# Reference slides

# Postlicensure 2-Dose Mumps Vaccine Effectiveness

## References

1. Vigen S et al., Euro Surveill 2016
2. Takla A et al., Human Vaccines & Immunotherapeutics 2014
3. Greenland K et al., Vaccine 2012
4. Deeks SL et al., CMAJ 2011
5. Livingston et al., Vaccine 2014
6. Snijders BEP et al., Vaccine 2012
7. Bangor-Jones RD et al., MJA 2009
8. Castilla J et al., Vaccine 2009
9. Dominguez A et al., Vaccine 2010
10. Marin M et al., Vaccine 2008
11. Schaffzin JK et al., Pediatrics 2007
12. Cohen C et al., EID 2007
13. Sartorius B et al., Euro Surveill 2005
14. Harling R et al., Vaccine 2005
15. Cardemil et al., NEJM 2017