Considerations for the Use of the 3rd Dose of MMR Vaccine For Persons at Increased Risk Because of a Mumps Outbreak and Proposed Recommendations

Mona Marin, MD, Division of Viral Diseases, CDC
On Behalf of ACIP Mumps Work Group

Advisory Committee on Immunization Practices Meeting
October 25, 2017
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 3rd 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 3rd 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*

*Marlow M. Grading of Recommendations Assessment, Development and Evaluation (GRADE): third dose of MMR vaccine. Presentation to ACIP meeting, Atlanta GA, October 25, 2017
Outline: Review of the Evidence

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

<table>
<thead>
<tr>
<th>Evidence/Factor</th>
<th>Question</th>
</tr>
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<tbody>
<tr>
<td><strong>Problem</strong></td>
<td>• What is the public health priority for the mumps program?</td>
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<td><strong>Benefits and harms</strong></td>
<td>• Do the desirable effects outweigh the undesirable effects?</td>
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<td><strong>Values</strong></td>
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<td>undesirable effects?</td>
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<tr>
<td><strong>Acceptability</strong></td>
<td>• Is the option acceptable to the key stakeholders?</td>
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<td><strong>Implementation</strong></td>
<td>• Is the option feasible to implement?</td>
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</table>
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

Burden of disease presented in: Marin M. Update on mumps epidemiology, United States. Presentation to ACIP meeting, Atlanta GA, October 25, 2017
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\(^1\) and decreased vaccine effectiveness with longer time since MMR2\(^2\)
  - Risk for mumps complications lower among MMR2 vaccinated case-patients vs. unvaccinated\(^3\)
  - 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\(^1\)
    - Lower quality antibodies: avidity, fewer memory B cells/failure to generate a strong memory B cell response\(^2\)
  - Neutralizing antibodies important for protection, persons with lower neutralization titer had increased risk for disease; no defined immunologic correlate of protection\(^3\)
  - Mean mumps antibody titers (both neutralizing and non neutralizing) decline over time in MMR2 vaccine recipients\(^4\)

- **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

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
    - Lower (~one-half) neutralizing antibody geometric mean titers to non-vaccine strains compared to Jeryl Lynn vaccine strain in MMR2 vaccine recipients
    - 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 ≥1:4

## Problem: Summary

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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?

<table>
<thead>
<tr>
<th>Population</th>
<th>Persons at increased risk for mumps because of an outbreak</th>
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<tbody>
<tr>
<td>Intervention</td>
<td>Third dose of MMR vaccine (MMR3)</td>
</tr>
<tr>
<td>Comparison</td>
<td>Two doses of MMR vaccine (MMR2)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Benefits</td>
</tr>
<tr>
<td></td>
<td>1. Prevention of mumps disease</td>
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<tr>
<td></td>
<td>2. Prevention of complications of mumps disease</td>
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<tr>
<td></td>
<td>3. Duration of protection</td>
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<tr>
<td></td>
<td>4. Immune response</td>
</tr>
<tr>
<td>Harms</td>
<td>1. Serious adverse events</td>
</tr>
<tr>
<td></td>
<td>2. Reactogenicity</td>
</tr>
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Bold font indicates outcomes considered by the WG “Critical” for GRADE analysis
## Benefits and Harms of MMR3

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Evidence reviewed presented in: Marlow M. Grading of Recommendations Assessment, Development and Evaluation (GRADE): third dose of MMR vaccine. Presentation to ACIP meeting, Atlanta GA, October 25, 2017
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%)

*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

### Benefits and Harms of MMR3

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<tr>
<td>Immune response</td>
<td>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</td>
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## Benefits and Harms of MMR3

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<td><strong>Serious adverse events</strong></td>
<td>No serious adverse events or vaccine-related health care visits in 14,368 MMR3 vaccine recipients</td>
</tr>
<tr>
<td><strong>Reactogenicity</strong></td>
<td>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)</td>
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## Balance of Benefits and Harms of MMR3: WG Interpretation

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<td>• Do the desirable effects outweigh the undesirable effects?</td>
<td>• The benefits of MMR3 outweigh the risks</td>
</tr>
<tr>
<td></td>
<td>• What is the certainty of the evidence for the critical outcomes?</td>
<td>• Data demonstrate short-term benefit of MMR3 vaccine for persons in outbreak settings</td>
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<tr>
<td></td>
<td></td>
<td>• No concerns for serious adverse events after MMR3; injection site reactions and non-serious systemic adverse events were mild and reported at low rates</td>
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<tr>
<td></td>
<td></td>
<td>• Evidence type: 4 for benefits, 2 for harms</td>
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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 3rd 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
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 Marlow M. Mumps outbreak experiences and practices. Results from college and university survey. ACIP Mumps WG, September 2017*
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

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 Marlow M. Mumps outbreak experiences and practices. Results from college and university survey. ACIP Mumps WG, September 2017
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 ≥1 mumps outbreak since Jan 1, 2016
    - 47% (20/43) reported recommending an outbreak/MMR3 dose during ≥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

*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

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</table>
| **Values**   | • How does the target population view the balance of desirable vs. undesirable effects? | Expert opinion:  
• Students and parents are concerned about mumps complications and potential for loss of productivity  
• Not concerned with serious adverse events |
| **Acceptability** | • Is the option acceptable to the key stakeholders?                     | • Stakeholders who implemented an outbreak/MMR3 recommendation had a positive experience overall, including a positive assessment of students’ and parents’ attitudes |
| **Implementation** | • Is the option feasible to implement?                                  | An ACIP recommendation would  
• Allow health departments to make more rapid decisions regarding use of MMR3  
• Increase access to MMR3 for persons identified at increased risk because of an outbreak  
Additional implementation guidance from CDC will be needed |
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 3rd Dose of MMR Vaccine Be Administered to Persons at Increased Risk for Mumps Because of an Outbreak?

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<td><strong>Benefits and harms</strong></td>
<td>Benefits outweigh the risks; evidence type is 4 for effectiveness and 2 for safety</td>
</tr>
<tr>
<td><strong>Values</strong></td>
<td>WG considered that persons in outbreak settings value prevention of: mumps, mumps complications, and loss of productivity</td>
</tr>
<tr>
<td><strong>Acceptability</strong></td>
<td>MMR3 vaccination was considered acceptable to students, parents, universities/schools, and health departments</td>
</tr>
<tr>
<td><strong>Implementation</strong></td>
<td>Providers and the target population have experience with MMR vaccination. Public health should be involved in identifying target groups at increased risk for mumps</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td>WG agreement that a 3rd dose of MMR vaccine would improve protection for persons at increased risk for mumps because of an outbreak</td>
</tr>
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</table>
WG Deliberations Regarding Proposed Recommendation
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

<table>
<thead>
<tr>
<th>Vaccination status</th>
<th>Existing recommendations to receive a dose (or 2) of MMR vaccine?*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unvaccinated</td>
<td>Yes</td>
</tr>
<tr>
<td>1-dose vaccinated</td>
<td></td>
</tr>
<tr>
<td>2-doses routinely recommended</td>
<td>Yes</td>
</tr>
<tr>
<td>1-dose routinely recommended</td>
<td>Yes, during outbreaks</td>
</tr>
<tr>
<td>2-dose vaccinated</td>
<td>No</td>
</tr>
<tr>
<td>3+-dose vaccinated</td>
<td>No†</td>
</tr>
<tr>
<td>Unknown vax status</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*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.
Acknowledgments

- Manisha Patel
- Mariel Marlow
- Paul Rota
- Mark Pallansch
- Don Latner
- Carole Hickman
- Janell Routh
- Adria Lee
- Amanda Cohn
- Jessica Leung

- ACIP Mumps Work Group
- CDC Mumps Team
WG Proposed Recommendations
Policy Question: Should a 3rd 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

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3. Greenland K et al., Vaccine 2012
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14. Harling R et al., Vaccine 2005
15. Cardemil et al., NEJM 2017