Grading of Recommendations Assessment, Development, and Evaluation (GRADE): Use of a Third Dose of Mumps Virus-Containing Vaccine in Persons at Increased Risk for Mumps Disease During an Outbreak

Introduction

In 1977, the Advisory Committee on Immunization Practices (ACIP) recommended one dose of mumps vaccine for all children aged ≥12 months (1). In 1989, in response to multiple measles outbreaks in the late 1980s, ACIP recommended routine administration of two doses of measles, mumps, rubella (MMR) [M-M-R II, Merck & Co., Inc] vaccine for children, with the first dose administered at ages 12 through 15 months and the second at ages 4 through 6 years (*2*). In addition to improved measles control, this policy led to substantial reduction in the number of mumps cases in the United States during the 1990s, which was sustained through 2005 (*3*). However, mumps outbreaks, primarily affecting populations with high coverage with two doses of MMR vaccine in midwestern states and colleges, occurred in 2006, prompting ACIP to formally recommend a routine 2-dose mumps vaccination policy for school-aged children (i.e., Kindergarten–grade 12) and adults at high risk (i.e., students at post-high school educational institutions, health care personnel, and international travelers) in 2006 (*4*). Despite this recommendation, mumps outbreaks continued to be reported throughout the United States. To assist state and local health departments in responding to mumps outbreaks, CDC issued guidance on use of a third dose of MMR vaccine in 2012 in specifically identified target populations.

As more evidence has accumulated after 2012, in October 2017 the Advisory Committee on Immunization Practices (ACIP) reviewed the evidence on vaccination with a third dose of mumps virus-containing vaccine. The policy question was "Should a third dose of mumps virus-containing vaccine be administered to persons at increased risk for mumps because of an outbreak?" Evidence of benefits and harms was evaluated in accordance with Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methods (*5*).

Methods for GRADE

The ACIP Mumps Work Group proposed beneficial and harmful outcomes of vaccination to consider, as well as the importance of these outcomes (critical vs. important).

A systematic review of Medline, Embase, Cochrane Library, CINAHL, Scopus and ClinicalTrials.gov, was conducted for studies in any language published from January 2000 to August 2017. The start date of January 2000 was selected because a large outbreak among persons with two doses of MMR vaccine was first reported in 2006 by the United States (*6*) and use of a third dose of mumps virus-containing vaccine was not considered before this and other large mumps outbreaks that occurred around the same time. We added five years as an additional capture period. Search terms are described in Table 1. Articles were included if they presented data on a third dose of mumps virus-containing vaccine and 1) reported primary data; 2) included data relevant to the outcome(s) being assessed; and 3) were not animal studies. The work group also pursued available unpublished data.

After review of the titles and abstracts (n=478), 50 studies were identified for further review. Of these, 34 studies did not report data on a third dose, 5 did not report on outcomes of interest, 1 study on a third dose was conducted only in immunocompromised children and 3 studies had results not yet reported or not found. We identified an additional 3 studies that were unpublished at the time of the work group assessment. A total of 10 studies reporting on critical and important outcomes were considered in the GRADE analysis. In this document, we summarize evidence from 7 studies that reported on critical outcomes (*7–13*). Studies included in the evaluation of important outcomes are provided in Supplementary Table 1 (*7*, *11–16*). In all studies, MMR vaccine was used as the third dose of mumps virus-containing vaccine.

Results

The benefits outcomes considered critical were preventing mumps disease and preventing complications of mumps disease and the harms outcome considered critical was occurrence of serious adverse events (SAEs) after vaccination (Table 2). Important outcomes included duration of protection, immune response, and reactogenicity.

Benefits outcomes

Three cohort studies reported on the outcome of preventing mumps disease. Characteristics and results of these studies are presented in Table 3. All studies were conducted in outbreak settings among populations with high two-dose coverage (i.e. >95%) and reported a lower attack rate in three dose MMR vaccine recipients compared with two dose recipients. Incremental vaccine effectiveness (VE) at 21 to 28 days post-vaccination ranged from 61% to 88% but only one estimate (78%, 95% CI 61%–88%) was significant ($p<0.001$). The GRADE evidence type for preventing mumps disease was 4 (Table 4).

For the outcome of preventing mumps complications, no studies reported on VE against mumps complications and the evidence type was not determined for this outcome (Table 4). However, it was considered that complications from mumps disease also are prevented when mumps disease is prevented by a third dose of MMR vaccine.

Harms outcome

One pre- and post- study and 4 case series studies reported on serious adverse events (SAE) of a third dose of MMR vaccine. Characteristics and results of these studies are presented in Table 3. SAE is defined as death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability. No SAEs were reported in 14,368 children and young adults vaccinated with a third dose. Two studies were based on passive reporting and 3 studies actively surveyed vaccine recipients. In addition, no healthcare visits for vaccination-related symptoms were reported in any of the studies. The GRADE evidence type for serious adverse events was 3 for the pre- and post- study and 2 for the cases series studies, and therefore the overall evidence type for this outcome was 2 (Table 4).

Summary

The evidence types supporting critical outcomes for use of third dose of mumps virus-containing vaccine in persons at increased risk for mumps disease because of an outbreak was determined to be 4 for preventing mumps, not determined for preventing mumps complications, and 2 for serious adverse events (Table 5). A third dose of MMR vaccine is effective in preventing mumps and no serious adverse events were reported in more than 14,000 third dose recipients. Together, the benefit of added protection of a third dose of mumps virus-containing vaccine outweighs the low risk for vaccine adverse events. After reviewing the results of the GRADE analysis and other data related to burden of disease, values attributed to benefits and harms from a third dose of MMR vaccine, acceptability, and implementation, the Advisory Committee on Immunization Practices (ACIP) recommended that persons previously vaccinated with two doses of a mumps virus-containing vaccine who are identified by public health authorities as being part of a group or population at increased risk for acquiring mumps because of an outbreak should receive a third dose of a mumps virus-containing vaccine to improve protection against mumps disease and related complications. Although studies evaluated for the GRADE analysis only assessed MMR vaccine, mumps virus-containing vaccine was used in the recommendation to include the measles, mumps, rubella, and varicella (MMRV) vaccine [ProQuad, Merck & Co., Inc] as an option for children aged 12 years or younger when a third dose mumps vaccination is indicated. The full recommendations for the use of mumps virus-containing vaccine in persons at increased risk for mumps because of an outbreak have been published in MMWR and are available at … *(link to MMWR policy note*).

Table 1. Use of a Third Dose of Mumps Virus-Containing Vaccine During Outbreaks: Literature Search Terms by Database

Database	Strategy
Medline (OVID) 1946-	[Mumps OR parotitis] AND [Vaccin* OR immuni?ation* OR MMR*] AND [(third ADJ5 (Dose* OR dosage)) OR (three ADJ5 (Dose* OR dosage)) OR (outbreak* ADJ5 (dose* OR dosage)) OR (additional ADJ5 (dose* OR dosage)) OR (booster* AND (outbreak* OR epidemic*)) OR (booster ADJ5 (dose* OR dosage)) OR military]
Embase (OVID) 1996-	[Mumps OR parotitis] AND [Vaccin* OR immuni?ation* OR MMR*] AND [(third ADJ5 (Dose* OR dosage)) OR (three ADJ5 (Dose* OR dosage)) OR (outbreak* ADJ5 (dose* OR dosage)) OR (additional ADJ5 (dose* OR dosage)) OR (booster* AND (outbreak* OR epidemic*)) OR (booster ADJ5 (dose* OR dosage)) OR military]
CINAHL (Ebsco) 1982-	[Mumps OR parotitis] AND [Vaccin* OR immuni?ation* OR MMR*] AND [(third N5 (Dose* OR dosage)) OR (three N5 (Dose* OR dosage)) OR (outbreak* N5 (dose* OR dosage)) OR (additional N5 (dose* OR dosage))

	OR (booster* AND (outbreak* OR epidemic*)) OR (booster N5 (dose* OR dosage)) OR military]
Cochrane 1800-	[mh mumps] OR (Mumps OR parotitis):ti,ab AND (Vaccin* OR immuni?ation* OR MMR*) AND (third NEAR/5 (Dose* OR dosage)) OR (three NEAR/5 (Dose* OR dosage)) OR (outbreak* NEAR/5 (dose* OR dosage)) OR (additional NEAR/5 (dose* OR dosage)) OR (booster* AND (outbreak* OR epidemic*)) OR (booster NEAR/5 (dose* OR dosage)) OR military
Scopus 1960-	TITLE-ABS-KEY(Mumps OR parotitis) AND TITLE-ABS-KEY(Vaccin* OR immuni?ation* OR MMR*) AND TITLE-ABS-KEY((third W/5 Dose*) OR (third W/5 dosage) OR (three W/5 Dose*) OR (three W/5 dosage) OR (outbreak* W/5 dose*) OR (outbreak* W/5 dosage) OR (additional W/5 Dose*) OR (additional W/5 dosage) OR (booster* AND (outbreak* OR epidemic*)) OR (booster W/5 dose*) OR (booster W/5 dosage) OR military) AND NOT INDEX(medline) AND NOT INDEX(embase)
Clinicaltrials.gov	(Mumps OR parotitis)

Table 2. Use of a Third Dose of Mumps Virus-Containing Vaccine During Mumps Outbreaks: Outcomes, Importance, and Data Availability

Outcome	Importance	Data available
Benefits		
Prevent mumps disease	Critical	Yes
Prevent mumps disease complications	Critical	No
Duration of protection	Important	No
Immune response	Important	Yes
Harms		
Serious adverse events	Critical	Yes
Reactogenicity	Important	Yes

Table 3. Use of a Third Dose of MMR Vaccine During Mumps Outbreaks: Characteristics and Results of Included Studies for Critical Outcomes

Author, year	Study design	Study population; setting	Comparison group	Benefit outcome (results)	Harm outcome (results)
Cardemil, 2017	Cohort	University students; outbreak	Two MMR dose vaccinated	Prevention of mumps disease (incremental VE=60%, 95% CI: 38%–74%)	None

Nelson, 2013*	Cohort	School children aged 9–14 yrs; outbreak	One or two MMR dose vaccinated	Prevention of mumps disease (incremental VE=61%, 95% CI: -243–95%)	Serious adverse events (0/533 doses administered)
Ogbuanu, 2012*†	Cohort	School children aged 11–17 yrs; outbreak	Two MMR dose vaccinated	Prevention of mumps disease (incremental VE=88%, 95% CI: -32–99%)	Serious adverse events (0/1,597 doses administered)
Albertson, 2016	Case series	University students and staff; outbreak	None	None	Serious adverse events (0/11,500 doses administered)
Aasheim, 2014	Case series	School children aged 12–19 years; outbreak	None	None	Serious adverse events(0/76 doses administered)
Abedi, 2012†	Case series	School children aged 11–17 years; outbreak	None	None	Serious adverse events (0/1,597 doses administered)
Routh, unpublished	Pre- and post-intervention	Young adults; non-outbreak	Pre-third MMR dose symptoms	None	Serious adverse events (0/662 doses administered)

VE=vaccine effectiveness; CI=confidence interval
***Considered case series studies for the outcome serious adverse events because the outcome was reported only for persons that received a third dose and not the comparison group**
†Studies reported survey data from the same study for the outcomes serious adverse events and are considered in the analysis as one study for this outcome

Table 4. Use of a Third Dose of MMR Vaccine During Mumps Outbreaks: Evidence Table for Critical Outcomes

Outcome	Design (# studies)	Initial Evidence	Risk of Bias	Inconsist-ency	Indirect-ness	Imprecis-ion	Other considerat-ions	Final Evidence type	Overall Evidence Type
Benefits									
Prevent mumps disease	Cohort (3)	3	Serious* (-1)	No serious	No serious	Serious† (-1)	None	4	4
Prevent complications of mumps disease	No studies	ND	ND	ND	ND	ND	ND	ND	ND
Harms									
Serious adverse events	Pre- and post- (1)	3	No serious	No serious	No serious	Unable to assess	None	3	2
	Case series (4)	3	No serious	No serious	No serious	Unable to assess	Yes‡	2	

Footnotes
ND=Not determined
***Selection bias; downgraded by 1**
†**The CI around the effect estimate are large or include both effect and non-effect; downgraded by 1**
‡**Strong strength of association. No reported serious adverse events in over 13,000 vaccinated persons; upgraded by 1**

Table 5. Considerations for Use of a Third Dose of Mumps Virus-Containing Vaccine During Mumps Outbreaks

Key factors	Comments
Balance between benefits and harms	A third dose of MMR vaccine is effective in preventing mumps. No evidence available but complications of mumps disease are prevented when mumps disease is prevented. There are no concerns for serious adverse events after vaccination with a third dose of MMR vaccine. ACIP considered that this evidence also would pertain to MMRV vaccine.
Evidence type for benefits and harms	**Benefits:** Prevent mumps disease: evidence type 4 Prevent complications of mumps disease: evidence type not determined **Harms:** Serious adverse events: evidence type 2

Supplementary Table 1. Use of a Third Dose of MMR Vaccine During Mumps Outbreaks: Characteristics of Included Studies for Important Outcomes

Author, year	Study design	Study population; setting	Comparison group	Benefit outcome	Harm outcome
Routh, unpublished	Pre- and post-intervention	Young adults; non-outbreak	Pre-third MMR dose symptoms	None	Reactogenicity
Latner, in press*	Repeated measures	Young adults; non-outbreak	Pre-third MMR dose titers	Immune response (IgG against whole virus, hemagglutinin-neuraminidase (HN) and nucleoprotein)	None
Fiebelkorn, 2014*	Repeated measures	Young adults; non-outbreak	Pre-third MMR dose titers	Immune response (plaque reduction neutralization (PRN) neutralizing antibody titers)	None

Nelson, 2013†	Cohort	School children aged 9–14 yrs; outbreak	One or two MMR dose vaccinated	None	Reactogenicity
Abedi, 2012‡	Case series	School children aged 11–17 years; outbreak	None	None	Reactogenicity
Ogbuanu, 2012†‡	Cohort	School children aged 11–17 yrs; outbreak	Two MMR dose vaccinated	None	Reactogenicity
Date, 2008	Repeated measures	University students seronegative for mumps; post-outbreak	Pre-third MMR dose titers	Immune response (IgG against whole virus)	None

***Studies used serum samples from same cohort but different antibody detection methods**
†Considered case series studies for the outcome reactogenicity because the outcome was reported only for persons that received a third dose and not the comparison group
‡Studies reported survey data from the same study for the outcome reactogenicity and are considered in the analysis as one study for this outcome

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