Grading of Recommendations Assessment, Development and Evaluation (GRADE): third dose of MMR vaccine

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GRADE Process

- **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 proposed recommendation and GRADE category

Policy Question: Should a third dose of MMR vaccine be administered to persons at increased risk for mumps because of an outbreak?

Population	Persons at increased risk for mumps because of an outbreak
Intervention	Third dose of MMR vaccine (MMR3)
Comparison	Two doses of MMR vaccine (MMR2)
Outcomes	• Mumps disease • Complications of mumps disease • Duration of protection • Immune response • Serious adverse events • Reactogenicity (non-serious local and systemic adverse events)

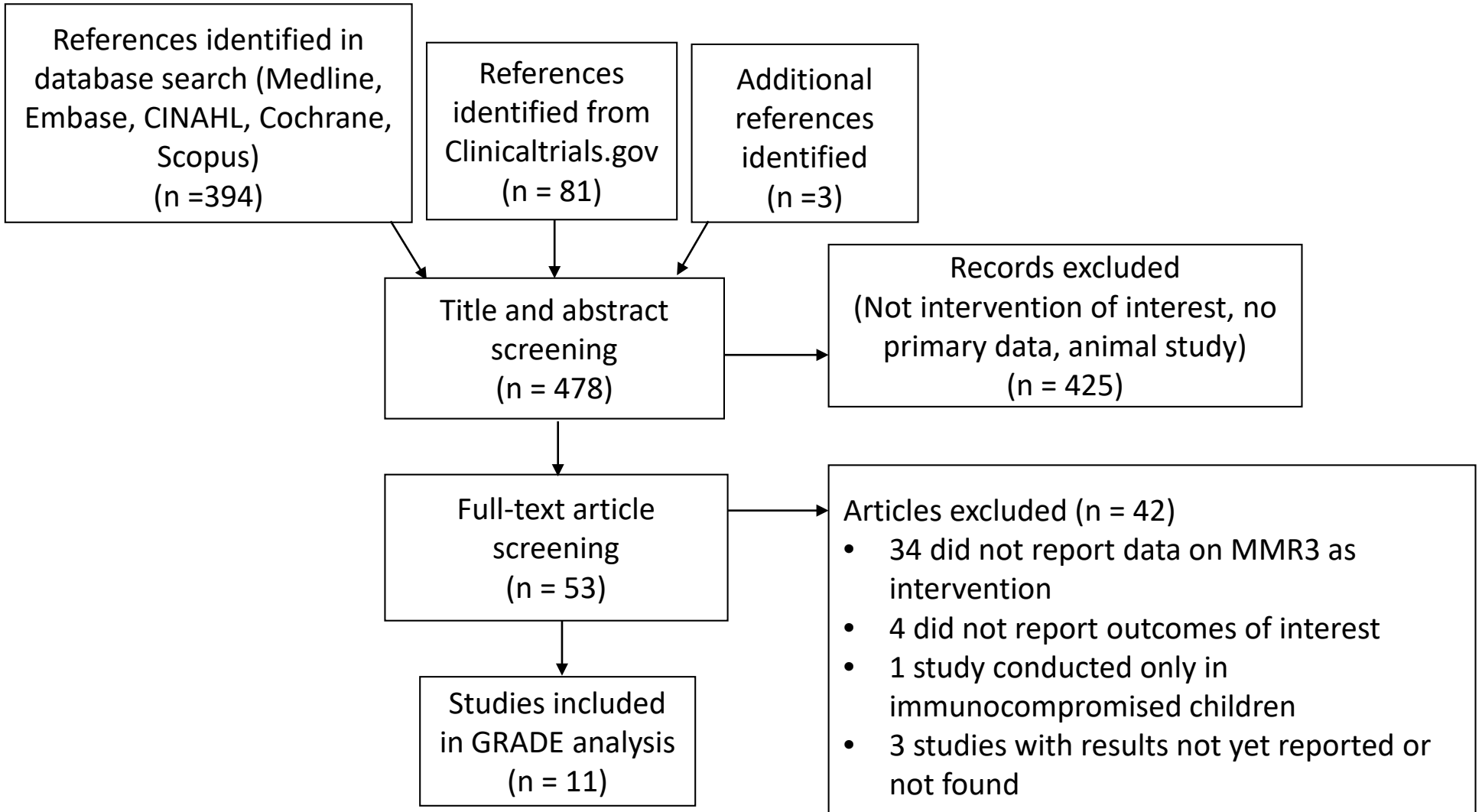
Importance of Benefits and Harms Outcomes

OUTCOME TYPE	OUTCOME	IMPORTANCE
Benefits	**Prevent mumps disease**	**Critical**
	Prevent complications of mumps disease	**Critical**
	Duration of protection	Important
	Immune response	Important
Harms	**Serious adverse events**	**Critical**
	Reactogenicity	Important

Evidence Retrieval

- Systematic review of studies in any language from PubMed, Embase, CINAHL, Cochrane, Scopus, and clinicaltrials.gov databases
- Efforts made to obtain unpublished or other relevant data
- Search string:
  - "mumps" or "parotitis";
  - and "vaccine" or "immunization" or "MMR";
  - and "third" or "three" or "outbreak" or "additional" or "booster" and "dose" or ("booster" and ("outbreak" or "epidemic")) or "military"
- Included articles presented primary data on
  - A third dose of MMR vaccine as the intervention
  - At least one outcome of interest
  - Were not animal studies

Evidence Retrieval



Evidence types

Initial Evidence Type	Study Design
1	Randomized controlled trials (RCTs) or overwhelming evidence from observational studies
2	RCTs with important limitations, or exceptionally strong evidence from observational studies
3	Observational studies, or RCTs with notable limitations
4	Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

GRADE of evidence for third dose of MMR vaccine: Benefits

Outcome #1: Vaccine effectiveness (VE) against mumps Characteristics of included studies

Study	Type	Population	Comparison	Outcomes measured	Site
Cardemil, 2017	Cohort	University students	MMR2	Attack rate (AR); incremental VE	University of Iowa
Nelson, 2013	Cohort	School children aged 9–14 yrs	≤MMR2	AR	Guam
Ogbuanu, 2012	Cohort	School children aged 11–17 yrs	MMR2	AR; incremental VE	Orange County, NY

- All studies conducted in outbreak settings among populations with high MMR2 coverage (>96%)
- Fiebelkorn et al. (2013) reported attack rate but used MMR3 as post-exposure prophylaxis among household contacts; not included

Outcome #1: VE against mumps
Estimates of effect

Study population	No. of subjects (# studies)	No. of MMR3 vaccinated subjects	No. of MMR3 vaccinated case-patients	AR in MMR2 (cases/1000 person-yr)	AR in MMR3 (cases/1000 person-yr)	VE of MMR3 (95% CI), 7 days	VE of MMR3 (95% CI), 21–28 days
University students	20,496 (1)	5,110	34	14.5	6.7	60% (38–74%)*†	78% (61–88%)*†
School children aged 11–17 years	2,178 (1)	1,723	1	4.8	0.6		88% (-32–99%)
School children aged 9–14 years	3,239 (1)	1,068	1	2.3‡	0.9		61% (-243–95%)§

**P* value <.001
†Calculated as (1-HR)*100; adjusted for 28 days post-vaccination and time since MMR2
‡Includes case-patients with <2 MMR doses
§Calculated by reviewers; not reported in article

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Outcome #1: VE against mumps
Type of Evidence

Outcome	Design (# of studies)	Initial evidence level	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	Evidence type
Prevention of mumps	Cohort (3)	3	**Serious**	No serious	No serious	**Serious**	None	4

- Downgraded for serious risk of bias that included selection bias
- Downgraded for serious imprecision given estimates had large confidence intervals of which some included no effect (< 0%)

Outcome #2: VE against mumps complications

- No studies reported on VE against mumps complications
- Not able to determine evidence type

Outcome #3: Duration of protection

- No clinical studies reported on duration of protection
- Not able to determine evidence type

Outcome #4: Immune response
Characteristics of included studies

Study	Type	Population	Comparison	Main outcomes	Site
Latner, unpublished*	Repeated measures study	Young adults; non-outbreak	Pre-MMR3 titers	IgG against whole virus, hemagglutinin-neuraminidase (HN) and nucleoprotein (NP) antigens	Marshfield
Fiebelkorn, 2014*	Repeated measures study	Young adults; non-outbreak	Pre-MMR3 titers	Plaque reduction neutralization (PRN) neutralizing antibody titers	Marshfield
Date, 2008	Repeated measures study	University students seronegative for mumps; post-outbreak	Pre-MMR3 titers	IgG against whole virus	University of Nebraska

*Studies used serum samples from same cohort but different antibody detection methods

Outcome #4: Immune response
Estimates of effect

Study	Antibody detection method*	No. of MMR3 vaccinated subjects	% seronegative participants		
			Baseline (pre-MMR3)	≤1 month†	>1 and ≤12 months†
Latner, 2017	Whole virus ELISA	656	0%	0%	0%
	NP ELISA	656	18%	4%	9%
	HN ELISA	656	42%	26%	36%
Fiebelkorn, 2014	PRN	656	0.8%	0%	0.2%
Date, 2008	Whole virus ELISA	19	100%	17%	8%

- All studies showed reduction in % of persons with seronegative titers at 1 month post-MMR3
- Antibodies levels were also significantly higher at 1 month

*Cutoffs for negative titers defined by authors

†Do not include loss to follow-up

NP=nucleoprotein; HN=hemagglutinin-neuraminidase; PRN=plaque reduction neutralization

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Immune response	Repeated measures study (3)	3	**Serious**	No serious	**Serious**	N/A	None	4

- Downgraded for serious risk of bias that included potential selection bias
- Downgraded for serious indirectness
  - No correlate of protection
  - Immunogenicity used as a proxy for effectiveness
  - Tested against vaccine strains vs circulating strain antigens
  - Studies conducted in non-outbreak settings

GRADE of Evidence for third dose of MMR vaccine: Harms

Outcome #5: Serious adverse events (SAE)
Characteristics of included studies

Study	Type	Population	Comparison	Data collection	Site
Routh, unpublished	Pre- and post- study	Young adults; non-outbreak	Pre-MMR3 symptoms	Prospectively monitored	Marshfield
Albertson, 2016	Case series	University students and staff	None	Passive reporting	University of Illinois at Urbana-Champaign
Aasheim, 2014	Case series	School children aged 12–19 years	None	Passive reporting	United Kingdom
Nelson, 2013	Case series†	School children aged 9–14 years	None	Retrospective survey	Guam
Abedi, 2012 and Ogbuanu, 2012*	Case series†	School children aged 11–17 years	None	Retrospective survey	Orange County, NY

* Studies conducted in Orange County reported same survey data

†Cohort study considered as case series because outcome only reported for MMR3

Outcome #5: Serious adverse events (SAE) Estimates of effect

- SAE defined as death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability

- No SAE reported in 14,368 children and young adults vaccinated with MMR3
  - 2 studies based on passive reporting (n=11,576)*
  - 3 studies actively surveyed vaccine recipients (n=2,792)†

- No healthcare visits for vaccination-related symptoms were reported

*Children aged 12–19 years and university students and staff
†Children aged 9–17 years and young adults

Outcome #5: Serious adverse events
Type of Evidence

Outcome	Design (# of studies)	Initial evidence level	Risk of bias	Inconsist-ency	Indirect-ness	Impreci-sion	Other consider-ations	Evidence type	Overall Evidence type
Serious adverse events	Pre- and post-study (1)	3	No serious	No serious	No serious	N/A	None	3	2
	Case series (4)	3	No serious	No serious	No serious	N/A	**Yes**	2	

- Cases series studies upgraded for strong strength of association

Outcome #6: Reactogenicity
Characteristics of included studies

Study	Type	Population	Comparison	Data collection	Site
Routh, unpublished	Pre- and post- study	Young adults; non-outbreak	Pre-MMR3 symptoms	Prospectively monitored	Marshfield
Nelson, 2013	Case series†	School children aged 9–14 years	None	Retrospective survey	Guam
Abedi, 2012 and Ogbuanu, 2012*	Case series†	School children aged 11–17 years	None	Retrospective survey	Orange County, NY

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Outcome #6: Reactogenicity
Estimates of effect — young adults (n=662)*

- Prospectively monitored adults aged 18–28 years
- Episodes of 14 symptoms solicited using daily diaries from 2 weeks before MMR3 to 4 weeks after MMR3
- 4 symptoms were significantly elevated among subjects after MMR3 compared with baseline

Symptom	Estimated net no. subjects w/≥1 episode post-MMR3	Estimated net % (95% CI) subjects w/≥1 episode post-MMR3	Median duration of symptom (IQR) in days
Joint problems	40	6 (3–9)	2 (1–5)
Headache	48	7 (4–11)	2 (1–4)
Diarrhea	61	9 (6–12)	1 (1–2)
Swollen glands	80	12 (7–18)	3 (1–5)

*Routh et al. (unpublished)

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Outcome #6: Reactogenicity
Estimates of effect — children

- Parents of children retrospectively surveyed on symptoms their child experienced ≤2 weeks post-MMR3 vaccination
- Survey conducted 2–4 months post-MMR3 campaigns

Study population	No. of subjects (No. of studies)	No. (%) MMR3 vaccinated w/symptoms within 2 weeks post-MMR3			
		Any symptom	Pain, redness, swelling at injection site	Joint aches	Dizziness or lightheaded-ness
Children aged 11–17 years*	533 (1)	32 (6)	12 (2)	13 (3)	12 (2)
Children aged 9–14 years†	1597 (1)	115 (7)	64 (4)	32 (2)	32 (2)

*Abedi et al. (2012) and Ogbuanu et al. (2012); †Nelson et al. (2013)

Outcome #6: Reactogenicity Type of Evidence

Outcome	Design (# of studies)	Initial evidence level	Risk of bias	Inconsist-ency	Indirect-ness	Impreci-sion	Other consider-ations	Evidence type	Overall evidence type
Reactogenicity	Pre- and post-study (1)	3	**Serious**	No serious	No serious	N/A	None	4	4
	Case series (2)	3	**Serious**	No serious	No serious	N/A	None	4	

- Pre- and post- study downgraded for serious risk of bias from potential observer effect
- Case series studies downgraded for serious risk of recall bias

Summary

GRADE Summary

Comparison: A third dose of MMR vaccine versus two MMR doses for persons at increased risk for mumps disease because of an outbreak

Outcome	Design (# of studies)	Findings	Evidence type
CRITICAL			
Prevent mumps	Cohort (3)	*MMR3 is effective in preventing mumps*	**4**
Prevent complications	No studies	*No evidence available*	**ND**
Serious adverse events	Pre- and post- study (1); case series (4)	*No concerns for serious adverse events after MMR3*	**2**
IMPORTANT			
Duration of protection	No studies	*No evidence available*	ND
Immune response	Repeated measures study (3)	*MMR3 provides short-term boost in antibodies and seroconverts most seronegative persons*	4
Reactogenicity	Pre- and post- study (1); case series (2)	*Non-serious adverse events reported at low rates; some symptoms were higher among young adults post-MMR3 compared with pre-MMR3 but were for short duration*	4

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- Wendy Carr
- Joanna Taliano
- ACIP Mumps Work Group
- MMRHP Mumps Team

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Thank you
Questions?