Priorix for Prevention of Measles, Mumps, and Rubella

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PICO and Policy Question

Should MMR vaccine (*Priorix*, GSK) be recommended as an option according to currently recommended schedules and off-label uses to prevent measles, mumps, and rubella?

Population	**Persons ≥6 months of age**
Intervention	**GSK Priorix**
Comparison	**Existing MMR vaccine licensed in the US (M-M-R II, Merck)**

Outcomes	• **Prevention of measles, mumps, and rubella**
	• **Short-term humoral immunity**
	• **Persistence of humoral immune response**
	• **Reactogenicity grade ≥3**
	• **Serious adverse events**
	  ◦ **Febrile seizures**
	  ◦ **Aseptic meningitis**
	  ◦ **Immune thrombocytopenic purpura**

MMR (Priorix, GSK) Vaccine

- **First licensed in Germany in 1997**
- **Approved in >100 countries outside US and over 400 million doses distributed worldwide**
  - Including all European countries, Canada, Australia; pre-qualified by WHO [2]
- **Priorix is considered fully interchangeable with M-M-R II in a number of countries**

Countries where Priorix is currently registered (n=97) [1]

[1] List of countries where Priorix is registered was provided by GSK

[2] WHO prequalification refers to use of international standards to comprehensively evaluate and determine whether vaccines are safe and effective. WHO also ensures the continued safety and efficacy of prequalified vaccines through regular re-evaluation, site inspection, targeted testing and investigation of any product complaints or adverse events following immunization.

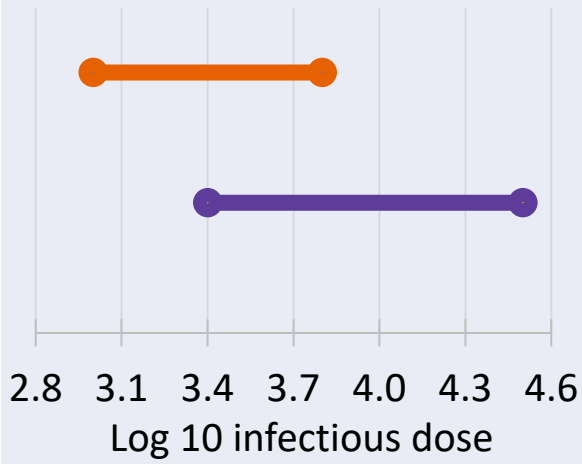
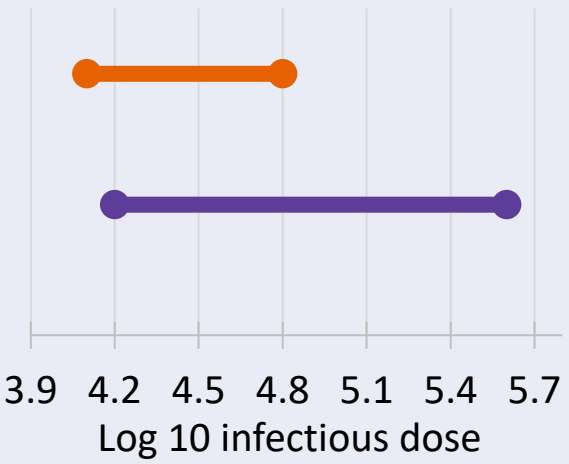
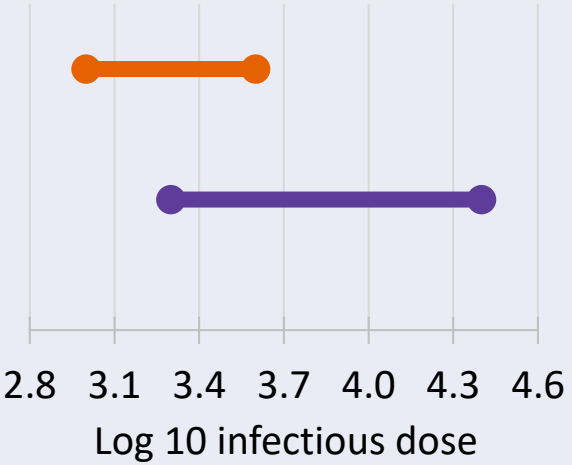
MMR Vaccine Components

	M-M-R II[1]	Priorix[2]	Component Similarity
Measles	**Enders' Edmonston** strain	**Schwarz** strain	**100% identical on a nucleotide level**
Mumps	**Jeryl Lynn™ (B level))**	**RIT4385**	**100% identical on a protein level[3]**
Rubella	**Wistar RA 27/3** strain	**Wistar RA 27/3** strain	**100% identical on a nucleotide level**

- **Inactive ingredients: Priorix does not contain gelatin**

[1] M-M-R II PI: http://www.merck.com/product/usa/pi_circulars/m/mmr_ii/mmr_ii_pi.pdf
[2] Priorix PI: https://www.fda.gov/media/158941/download
[3] GSK's RIT4385 (JL1 clone) and Merck's JL1 component of the Jeryl Lynn strain

MMR Minimum and Maximum Release Potencies

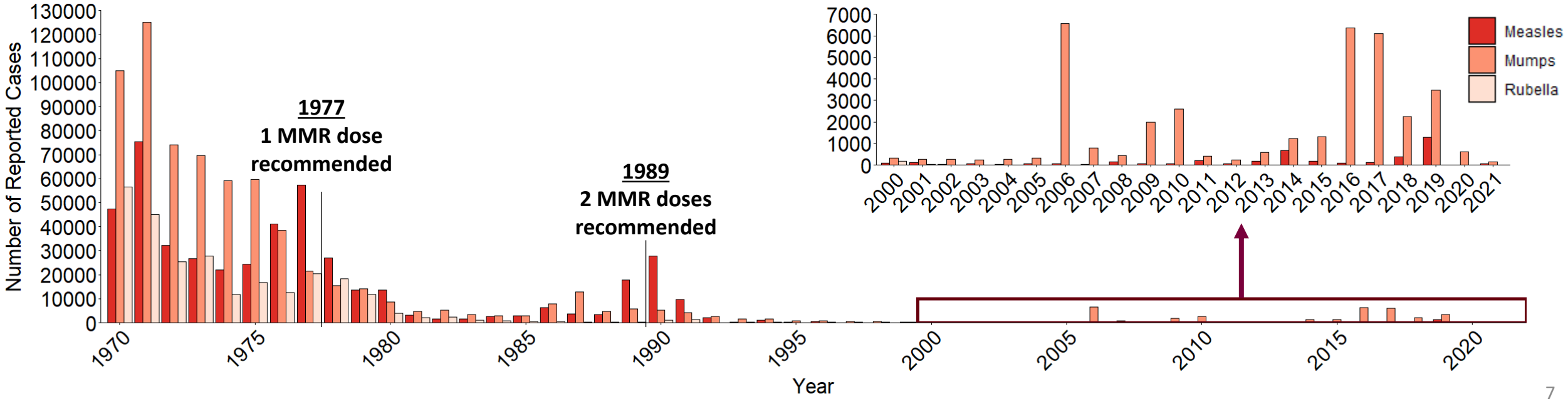
	Measles	Mumps	Rubella
M-M-R II	≥ $10^{3.0}$ – $10^{3.8}$ $TCID_{50}$	≥ $10^{4.1}$ – $10^{4.8}$ $TCID_{50}$	≥ $10^{3.0}$ – $10^{3.6}$ $TCID_{50}$
M-M-R II Priorix (US)			
Priorix (US)	≥ $10^{3.4}$ – $10^{4.5}$ $CCID_{50}$	≥ $10^{4.2}$ – $10^{5.6}$ $CCID_{50}$	≥ $10^{3.3}$ – $10^{4.4}$ $CCID_{50}$
Priorix (Other)	≥ $10^{3.0}$	≥ $10^{3.7}$	≥ $10^{3.0}$

- **Minimum and maximum viral potency titers are defined during clinical development to ensure efficacy at minimum potency and safety at maximum potency**

Evidence to Recommendations Framework (EtR) Domains

Public Health Problem: Is the prevention of measles, mumps, and rubella a problem of public health importance?

- Attaining and maintaining high 2-dose MMR coverage has led to measles and rubella elimination in the US, and low levels of mumps
- Despite high 2-dose vaccine coverage, measles and mumps continue to cause locally acquired and importation-related cases and outbreaks



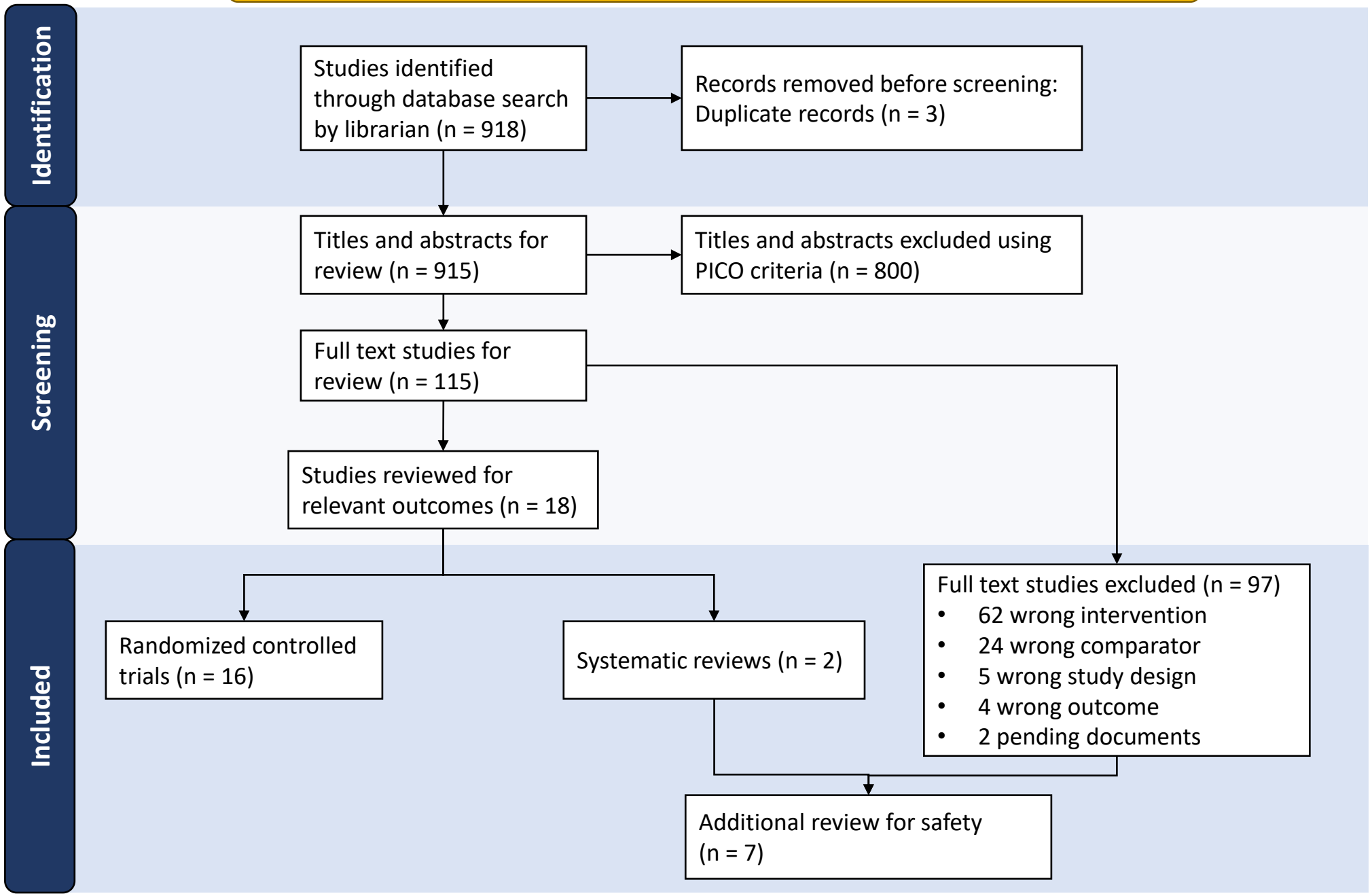
Should MMR vaccine (Priorix, GSK) be recommended as an option according to currently recommended schedules and off-label uses to prevent measles, mumps, and rubella?

Domain	Question	Work Group Judgments
Benefits and Harms	For prevention of measles, mumps and rubella (seroprotection), how substantially different are the desirable anticipated effects of Priorix compared with M-M-R II? *How substantial are the desirable anticipated effects?*	
	For the outcomes of serious and mild adverse events, how substantially different are the undesirable anticipated effects of Priorix compared with M-M-R II? *How substantial are the undesirable anticipated effects?*	
	Does the balance between desirable effects and undesirable effects favor Priorix or M-M-R II? *Do the desirable effects outweigh the undesirable effects?*	

Literature Review

- **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:**
  - "Measles-Mumps-Rubella Vaccine"
  - and ("Priorix" or "MMR vaccine" or ("GlaxoSmithKline*" or "GSK") and "MMR*") or "GSK-MMR" or "MMR-RIT" or "SB-MMR")
  - and "Safe*" or "effective*" or "efficacy" or "immun*" or "interchangeab*" or "inter-changeab*" or "adverse" or "M-M-R II" or "Merck" or "evidence*" or ("review" or "meta*")
- **Included articles were limited to:**
  - Randomized controls trials or systematic reviews and meta-analyses
  - Vaccine given to persons ≥6 months of age
  - At least 1 dose of MMR (Priorix) vaccine as the intervention
  - At least 1 dose of MMR (M-M-R II) vaccine as the comparator
  - At least one outcome of interest
  - Were not animal studies

PRISMA Flow Diagram: Identification of Priorix* studies



*Priorix is also known as: SB-MMR, MMR-RIT

Safety

Characteristics of RCTs at US dose (n = 4)[1-4]

- **Participants were from USA (90%) and Sweden (10%)**
- **2893 total participants with according-to-protocol results**
  - 1960 Priorix (68%)
  - 933 M-M-R II (32%)
- **Ages***
  - 12-15 months: n = 2594 (90%)
  - 2-4 years: n = 752 (26%)
  - 12 years: n = 299 (10%)
- **No significant difference in race and ethnicity between Priorix and M-M-R II groups**
- **Outcomes measured**
  - Serious adverse events (SAEs) (n = 4)
  - Reactogenicity ≥3 (n=3)

* Because Berry 2017 is a subset of Mufson 2014, age groups add up to > 100%

1. Mufson, M. A. et al. Safety and Immunogenicity of Human Serum Albumin-Free MMR Vaccine in US Children Aged 12–15 Months. J Pediatric Infect Dis Soc 4, 339–348 (2015).
2. Berry, A. A. et al. Two-year antibody persistence in children vaccinated at 12–15 months with a measles-mumps-rubella virus vaccine without human serum albumin. *Hum Vacc Immunother* (2017).
3. Gothefors, L., et al. Immunogenicity and Reactogenicity of a New Measles, Mumps and Rubella Vaccine When Administered as a Second Dose at 12 y of Age. *Scand J Infect Dis* (2009).
4. MMR-162 et al. Safety and immunogenicity of an upper-range release titer measles-mumps-rubella vaccine in children vaccinated at 12 to 15 months of age: a phase III, randomized study. *Hum Vacc Immunother* (2018).

Summary of Serious Adverse Events (n = 4 RCTs)

- **Priorix shows a similar safety profile to M-M-R II**
  - Follow up time was 40 days to 6 months across the studies
  - Frequency of vaccine related SAEs
    - Priorix: 0%-0.2%
    - M-M-R II: 0%-0.3%
- **Vaccine-related SAEs identified in clinical trials**
  - Immune thrombocytopenic purpura (Priorix: n = 1; M-M-R II: n = 1)
  - Inguinal adenitis (Priorix: n = 1)
  - Complex febrile seizure (M-M-R II: n = 1)

Conditions of Interest From ACIP and WG

- Febrile seizures
- Aseptic meningitis
- Immune Thrombocytopenic Purpura (ITP)

Rates of Febrile Seizures

- **The rate of febrile seizures is highest in the 6 to 11 days following vaccination for all[1] MMR vaccines**
  - The rate for febrile seizures after administration of MMR vaccines is 3.3[2]-8.7[3] per 10,000 doses

Study	Age	Febrile seizure rates per 10,000 doses 6-11 days post dose 1*	
		Priorix (n = 8386)	M-M-R II (n = 3561)
MMR-157, MMR-160, MMR-161, MMR-162	12-15 months	9.5 [95% CI 4.0,19.0]	14.8 [95% CI 2.0,22.0]

- **Priorix clinical trials:**
  - Rate of febrile seizures were not significantly different between Priorix and M-M-R II recipients
  - Timing of fever was comparable for both vaccines across all studies with majority observed 5-12 days post vaccination

[1] Priorix, M-M-R II, Urabe-9 containing MMR

[2] Miller, E. *et al.* Risks of Convulsion and Aseptic Meningitis following Measles-Mumps-Rubella Vaccination in the United Kingdom. *Am J Epidemiol* **165**, 704–709 (2007).

[3] Farrington, P. *et al.* A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. *Lancet* **345**, 567–569 (1995).

*Secondary analysis based on 6-11 day period

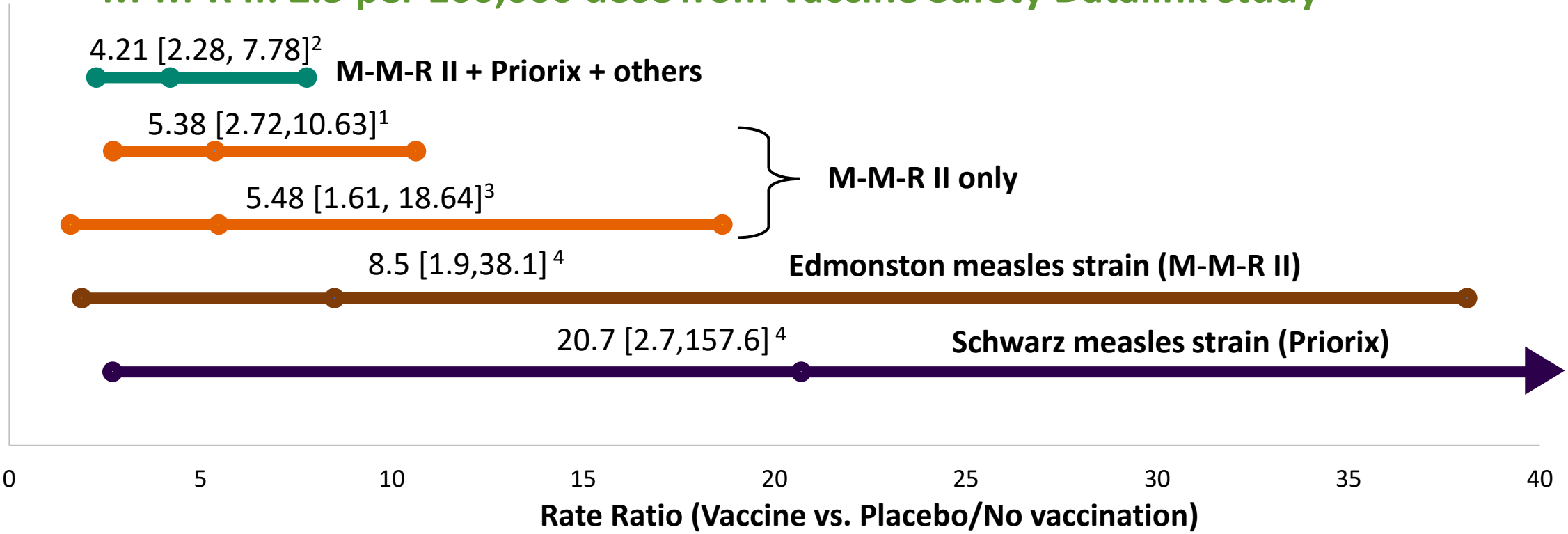
Aseptic Meningitis

- **Miller 2007** [1]
  - Active surveillance for aseptic meningitis and mumps meningitis in the 15-35 days post vaccination, 1998-2004
  - **Zero** cases of aseptic meningitis as identified by ICD-9/10 code and chart review out of 99,177 doses of Priorix given
  - **Zero** cases of laboratory-confirmed mumps meningitis out of 1,612,360 doses of Priorix given
  - Based on the number of doses and cases observed in the study time frame, allowed exclusion of risks as rare as **1 in 437,000 doses** for laboratory-confirmed mumps meningitis with Priorix
- **WHO Global Advisory Committee on Safety: "not aware of any cases of virologically proven aseptic meningitis following Jeryl–Lynn vaccine"** [2]
- **DiPietrantonj 2021 (Cochrane Review)** [3]
  - No evidence of association was found for vaccines prepared with mumps Jeryl Lynn strains

[1] Miller, E. *et al.* Risks of Convulsion and Aseptic Meningitis following Measles-Mumps-Rubella Vaccination in the United Kingdom. *Am J Epidemiol* 165, 704–709 (2007).
[2] World Health Organization Global Advisory Committee on Vaccine Safety. *WER* **32**, 282–283 (2003).
[3] DiPetrantonj C, et al. Vaccines for measles, mumps, rubella, and varicella in children. Cochrane Database of Systematic Reviews 2021.

Immune Thrombocytopenic Purpura (ITP)

- ITP is associated with receipt of live attenuated measles vaccines
- 4 RCTs at the US dosage
  - Priorix: 1 case in 4 RCTs (n = 1960)
  - M-M-R II: 1 case in 4 RCTs (n = 933)
- M-M-R II: 2.5 per 100,000 dose from Vaccine Safety Datalink study[1]



[1] France, E. K. *et al.* Risk of Immune Thrombocytopenic Purpura After Measles-Mumps-Rubella Immunization in Children. *Pediatrics* **121**, e687–e692 (2008).

[2] Pietrantonj, C. D., Rivetti, A., Marchione, P., Debalini, M. G. & Demicheli, V. Vaccines for measles, mumps, rubella, and varicella in children. *Cochrane Db Syst Rev* **2021**, CD004407 (2021).

[3] O'Leary, S. T. *et al.* The Risk of Immune Thrombocytopenic Purpura After Vaccination in Children and Adolescents. *Pediatrics* **129**, 248–255 (2012).

[4] Perez-Vilar, S. *et al.* Enhancing global vaccine pharmacovigilance: Proof-of-concept study on aseptic meningitis and immune thrombocytopenic purpura following measles-mumps containing vaccination. *Vaccine* **36**, 347–354 (2018).

Summary of Conditions of Interest From ACIP and WG

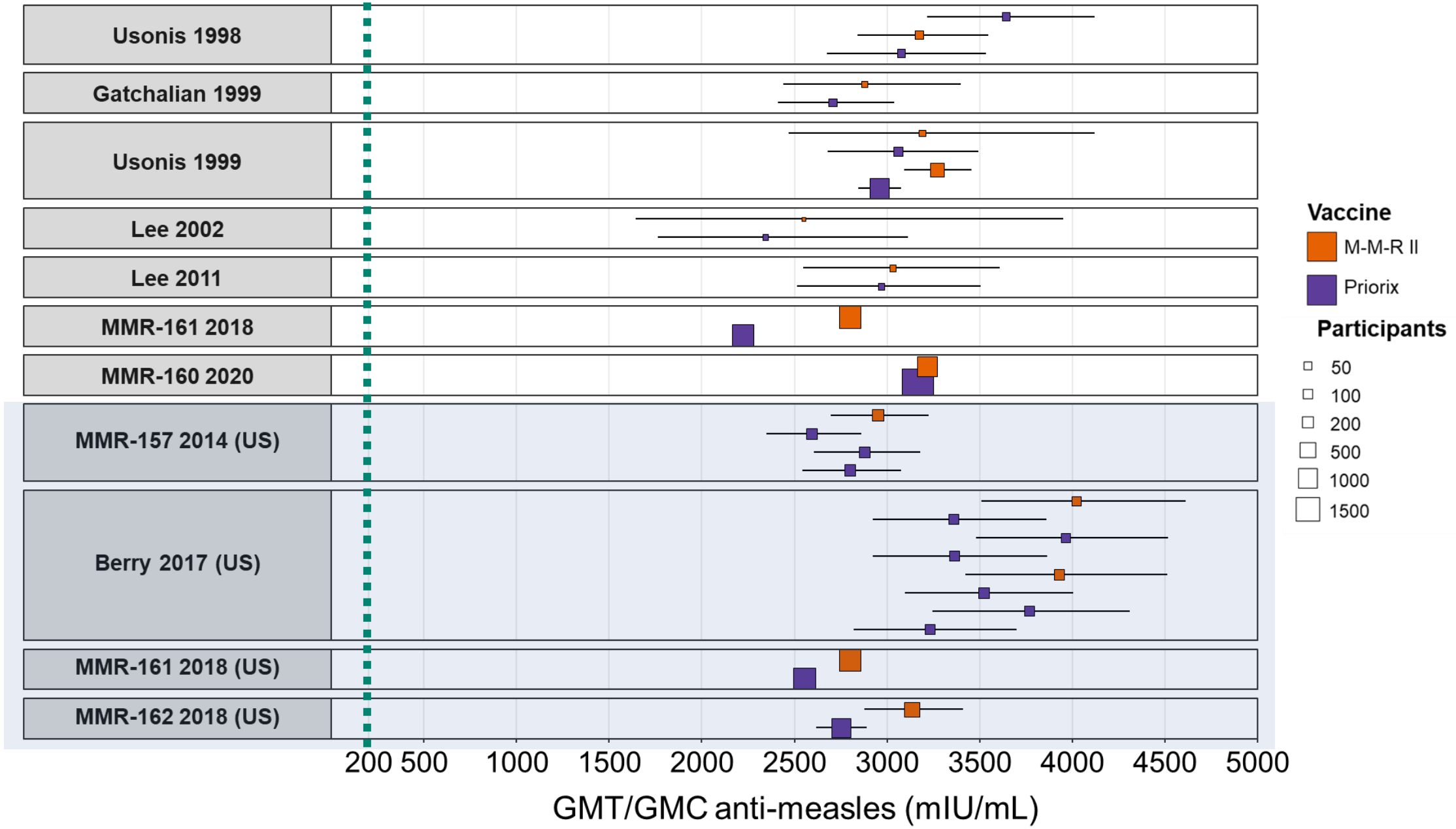
- **Febrile seizures**
  - Similar rate between Priorix and M-M-R II
- **Aseptic meningitis (mumps meningitis)**
  - No evidence of association for vaccines prepared with Jeryl Lynn strains
  - Exclusion of risks as rare as 1 in 437,000 doses
- **Immune Thrombocytopenic Purpura**
  - Limited data – Similar between Priorix and M-M-R II

Immunogenicity

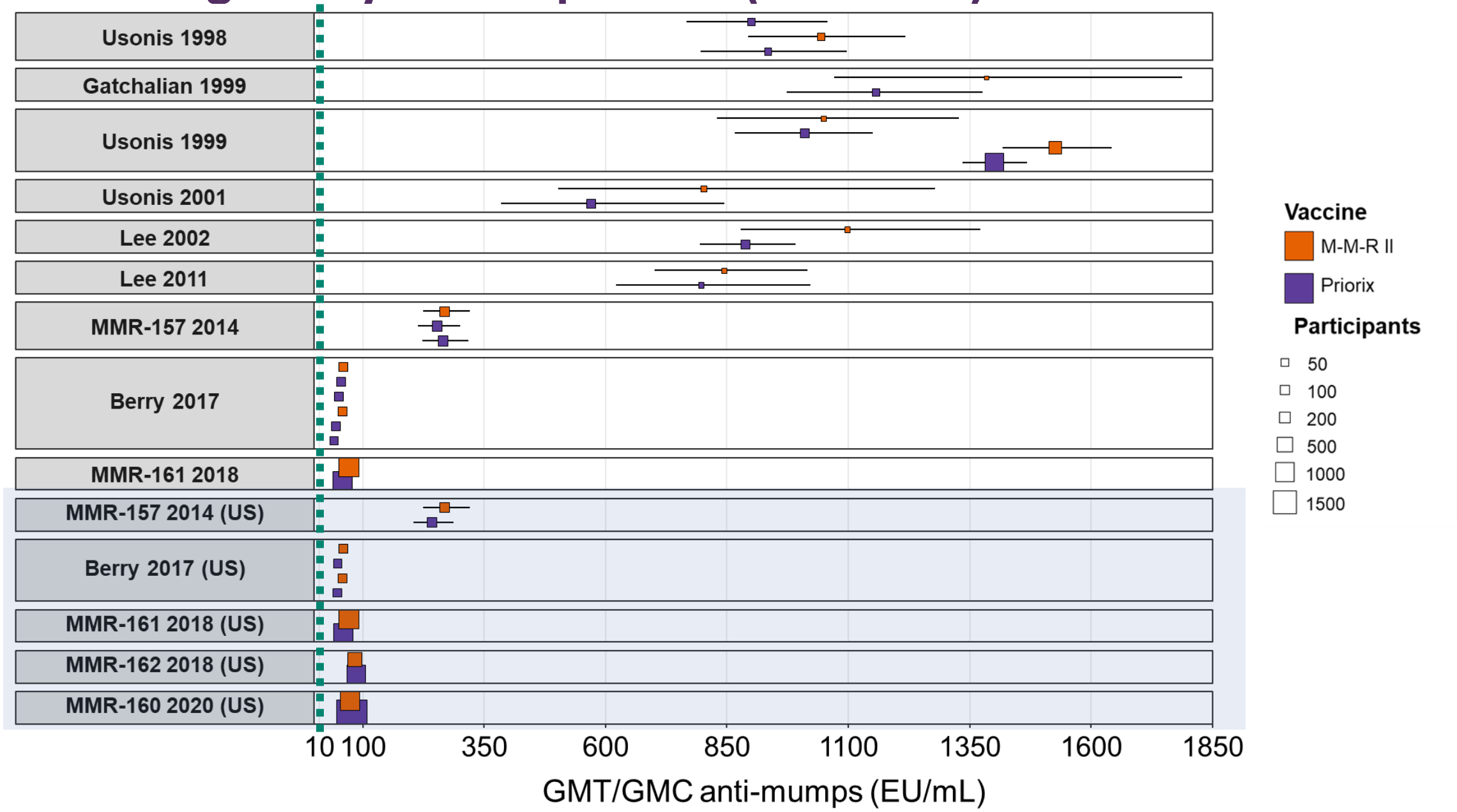
Immunogenicity

- **13/16 RCTs presented immunogenicity data**
  - Seroconversion after first dose of MMR
  - Seroconversion after second dose of MMR
  - Geometric mean concentration (GMC) after first dose of MMR
  - GMC after second dose of MMR

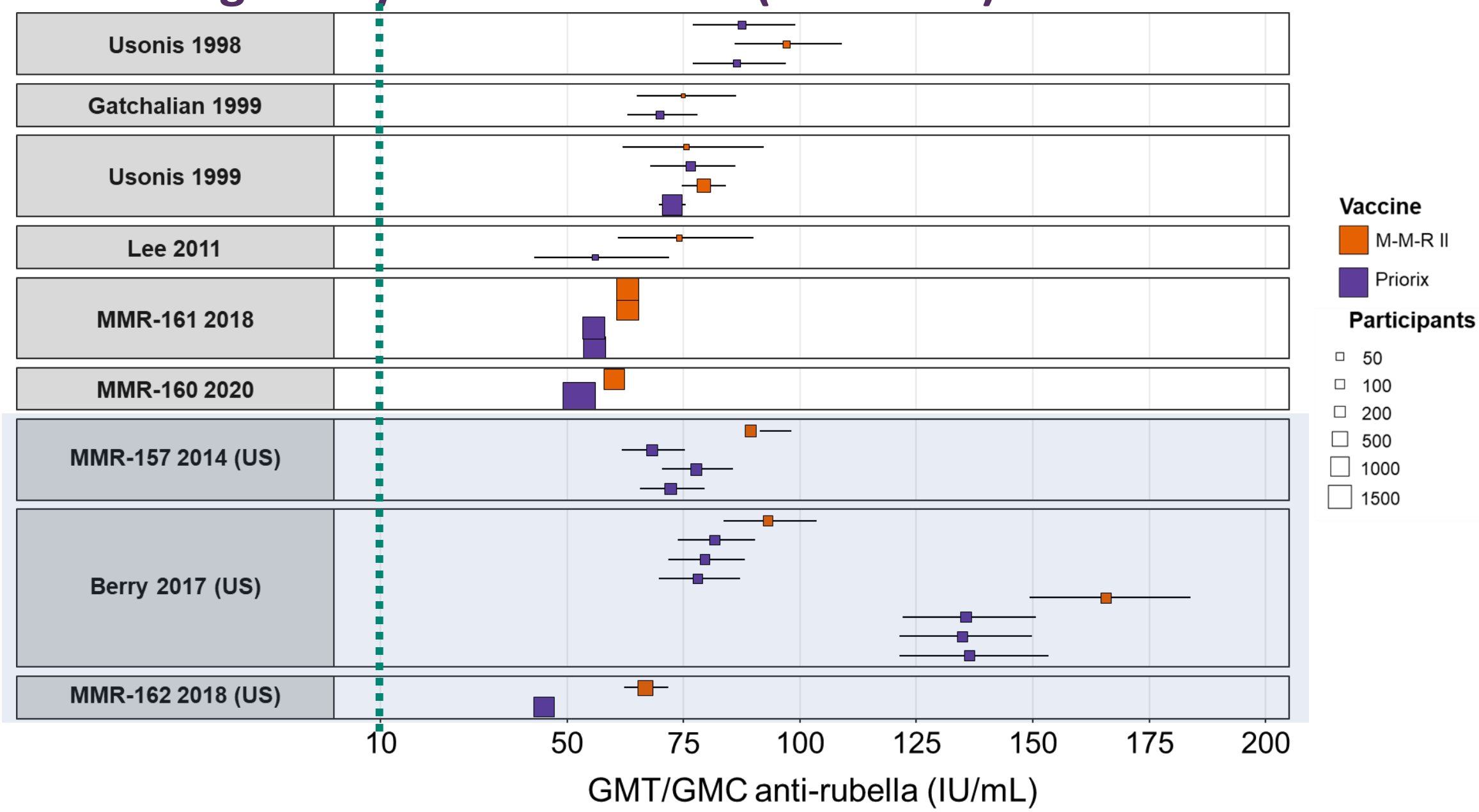
Immunogenicity – Measles GMC (first dose)



Immunogenicity – Mumps GMC (first dose)



Immunogenicity – Rubella GMC (first dose)



Immunogenicity Summary

- **Studies conducted with US dosage**
  - No significant difference in GMC for measles, mumps, or rubella between Priorix and M-M-R II

- **Studies at dosage lower than US**
  - All studies showed GMC higher than correlate of protection for measles and rubella and the sero-response threshold for mumps
  - 10 of 13 studies showed no statistically significant difference between anti-mumps GMC levels

- **No significant difference for second dose between Priorix and M-M-R II for any antigen at any potency (n = 4)**

Benefits and Harms: how substantial are the desirable and undesirable anticipated effects are of Priorix as compared with M-M-R II?

Domain	Question	Work Group Judgments
Benefits and Harms	For prevention of measles, mumps and rubella (seroprotection), how substantially different are the desirable anticipated effects of Priorix compared with M-M-R II? *How substantial are the desirable anticipated effects?*	**Minimal**
	For the outcomes of serious and mild adverse events, how substantially different are the undesirable anticipated effects of Priorix compared with M-M-R II? *How substantial are the undesirable anticipated effects?*	**Minimal**
	Does the balance between desirable effects and undesirable effects favor Priorix or M-M-R II? *Do the desirable effects outweigh the undesirable effects?*	**Favors Both**

Feasibility and Acceptability

- Is Priorix as an option for MMR vaccination feasible to implement?
- Is Priorix acceptable to key stakeholders?

Feasibility

- **Occasional shortages of routine recommended vaccines including MMR from 2000-2003[1]**
  - Due to two voluntary interruptions to manufacturing operations by only US manufacturer (Merck)[2]
- **Redundancy in supply is critical component of sustainable public health[3]**
- **MMRV accounts for ~13% (5%-24%) of first dose and ~80% (52%-98%) of second dose[4]**
- **An additional MMR vaccine (Priorix) that is safe and non-inferior to the existing MMR (M-M-R II) vaccine could be beneficial in maintaining measles and rubella elimination and mitigating mumps outbreaks in the United States**

[1] Santibanez TA, et al. Differential Effects of the DTaP and MMR Vaccine Shortages on Timeliness of Childhood Vaccination Coverage. American Journal of Public Health. 2006
[2] Shortage of varicella and measles, mumps and rubella vaccines and interim recommendations from the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2002.
[3] Executive Order 14001 "On a Sustainable Public Health Supply Chain" - https://www.phe.gov/Preparedness/legal/Documents/National-Strategy-for-Resilient-Public-Health-Supply-Chain.pdf
[4] CDC, unpublished data

Focus Group with Immunization Managers – May 2022

- **Majority of VFC* and vaccine programs order based on providers' demand**

- **Not considered a barrier**
  - Adding Priorix into routine immunization program - "Very used to managing multiple brands and presentations with similar vaccines."
  - Vaccine access, distribution, differences in storage and handling
  - Implementation of communication and education strategies

- **Additional considerations**
  - Welcomed the idea of having another brand
  - Benefit of having a gelatin-free vaccine for religious groups with objections to gelatin

* Vaccines for Children Program

Key Findings from Survey of Pediatric and Family Medicine Practitioners, May 24 – June 6, 2022

- **Respondents**
  - 400 US Pediatricians
  - 400 US Family Physicians

- **Key Findings**
  - A common concern for pediatricians was the possibility they would not be able to use the two vaccines as “mix-and-match”
  - ~27% of each specialty reported having at least one patient who did not receive an MMR vaccine due to allergy to a vaccine component
    - 30%-40% due to reported allergy to gelatin
  - Most (69%) of pediatricians have used MMR for patients aged <1 year

Work Group Considerations on Interchangeability

- **Previously presented studies[1] show non-inferior immune responses and similar safety profile for individuals receiving a first dose with M-M-R II or ProQuad (MMRV) and second dose Priorix**
- **Countries where Priorix is fully interchangeable with M-M-R II (MMRVaxPro in Europe)**
  - Australia, Canada, Denmark, France[2], New Zealand, United Kingdom, Ireland
  - WHO considers all commercially available live attenuated measles vaccines to be interchangeable for the prevention of measles[3]
- **Additional considerations**
  - Per FDA licensure: "PRIORIX may be administered as a second dose to individuals who have received a first dose of another measles, mumps and rubella virus-containing vaccine."
  - European Medicines Agency allows vaccination with Priorix in individuals who have been previously vaccinated with a different MMR (or monovalent) vaccine[4]
- **Limited data on Priorix first dose and M-M-R II or ProQuad (MMRV) as second dose**
  - No safety or immunogenicity differences identified in currently available data[5]

[1] MMR-158 2019, Abu-Elyazeed 2018

[2] Even though interchangeable, France recommends completing the series with the same vaccine

[3] https://cdn.who.int/media/docs/default-source/immunization/position_paper_documents/measles/who-pp-measles-vaccine-presentation-2017.pdf?sfvrsn=a592691c_2

[4] https://www.ema.europa.eu/en/documents/referral/priorix-article-30-referral-annex-iii_en.pdf

[5] Abu-Elyazeed, R. *et al.* Immunogenicity and safety of a second dose of a measles-mumps-rubella vaccine administered to healthy participants 7 years of age or older: A phase III, randomized study. 2018. and personal communication 2022.

Feasibility and Acceptability

Domain	Question	Work Group Judgments
Public Health Problem	Is the prevention of measles, mumps, and rubella a problem of public health importance? *Is the problem of public health importance?*	**Yes**
Benefits and Harms	For prevention of measles, mumps and rubella (seroprotection), how substantially different are the desirable anticipated effects of Priorix compared with M-M-R II? *How substantial are the desirable anticipated effects?*	**Minimal**
	For the outcomes of serious and mild adverse events, how substantially different are the undesirable anticipated effects of Priorix compared with M-M-R II? *How substantial are the undesirable anticipated effects?*	**Minimal**
	Does the balance between desirable effects and undesirable effects favor Priorix or M-M-R II? *Do the desirable effects outweigh the undesirable effects?*	**Favors Both**
Acceptability	Is Priorix acceptable to key stakeholders?	**Yes***
Feasibility	Is Priorix feasible to implement?	**Yes***

*Differences in off-label uses and interchangeability recommendations could negatively affect both acceptability and feasibility

Equity

Domain	Question	Work Group Judgments
Public Health Problem	Is the prevention of measles, mumps, and rubella a problem of public health importance? *Is the problem of public health importance?*	**Yes**
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	Does the balance between desirable effects and undesirable effects favor Priorix or M-M-R II? *Do the desirable effects outweigh the undesirable effects?*	**Favors Both**
Acceptability	Is Priorix acceptable to key stakeholders?	**Yes**
Feasibility	Is Priorix feasible to implement?	**Yes**
Equity	What would be the impact of the Priorix compared to M-M-R II on health equity?	**Probably no impact**

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Acceptability	Is Priorix acceptable to key stakeholders?	**Yes**
Feasibility	Is Priorix feasible to implement?	**Yes**
Equity	What would be the impact of the Priorix compared to M-M-R II on health equity?	**Probably no impact**
Values	**Based on similarities of schedule, anticipated harms and benefits, and VFC costs, ACIP MMR Work Group perceived that these domains of Values and Resource Use for Priorix are comparable with Values and Resource Use of M-M-R II.**	
Resource Use		

EtR Balance of Consequences

Based on EtR considerations, Priorix and M-M-R II vaccines are closely balanced, and therefore the Work Group judgment on adding Priorix as an option for MMR vaccination is as follows:

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences is *closely balanced* or *uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings	There is insufficient evidence to determine the balance of consequences

Clinical considerations

- **Given the similarities in dosage and vaccine components, the evidence from the clinical trials, and literature review, the Work Group considers Priorix and M-M-R II :**
  - Fully interchangeable - including all off-label uses

Routine recommendation	Off-label recommendations
• Prevention of measles, mumps, and rubella in individuals 12 months of age and older	• Children aged 6-11 months (planning to travel/live abroad or during outbreaks) [1] • 3rd dose during mumps outbreaks[2] • Measles post-exposure prophylaxis

  - Priorix may be administered in any situation in which a measles, mumps, and rubella-containing vaccine is indicated

[1] https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6204a1.htm
[2] https://www.cdc.gov/mmwr/volumes/67/wr/mm6701a7.htm

References (1)

1. (CDC), C. for D. C. and P. Shortage of varicella and measles, mumps and rubella vaccines and interim recommendations from the Advisory Committee on Immunization Practices. *Mmwr Morbidity Mortal Wkly Rep* 51, 190–1 (2002).
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Thanks

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