Annexes to the SAGE 2024 mumps vaccines position paper

Grading of evidence

Evidence-to-decision tables

Contents

Background

Annexes 1–9 contain tables that summarize the Grading of Recommendations Assessment, Development and Evaluation (GRADE). Annex 10 contains the SAGE Evidence-to-Decision tables.

The 2021 Cochrane review was used for identification of the studies for effectiveness and safety of mumps-containing vaccines using the Jeryl–Lynn and Leningrad–Zagreb strains, regardless of number of doses. Quality of evidence was determined by reviewing GRADE from the original papers included in the Cochrane review.

Annex 1. GRADE table: Efficacy of mumps-containing vaccines: Cohort studies – Jeryl–Lynn strain, 1 dose

Population: Children aged 0–15 years

Intervention: 1 dose of mumps-containing vaccine with Jeryl–Lynn strain

Comparison: No vaccination/unvaccinated

Outcomes: Clinical and laboratory-confirmed mumps disease

Question: Should vaccination with 1 dose of mumps-containing vaccine with the Jeryl–Lynn strain, vs no vaccination, be used for the prevention of mumps disease?

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mumps vaccine**	**Unvaccinated**	**Relative (95% CI)**	**Absolute**	**Quality of evidence**
6	Observational studies[a]	No serious risk of bias	Serious inconsistency[b]	No serious indirectness	No serious imprecision	Large sample size[c]	68/6690	175/3225	RR: 0.28 (0.13–0.62)	–	⨁⨁◯◯ LOW[d]

CI = confidence interval; RR = relative risk.

[a] Cohort studies: Jeryl–Lynn strain, 1 dose; [b] $I^2 = 81\%$; [c] RR: 0.28 (0.13–0.62) with 9915 participants; [d] In the Cochrane review, the quality was graded "Moderate", but was downgraded here because of serious inconsistency and upgraded for low RR.

References

- Greenland K, Whelan J, Fanoy E, Borgert M, Hulshof K, Yap KB, et al. Mumps outbreak among vaccinated university students associated with a large party, the Netherlands 2010. Vaccine. 2012;30(31):4676–80 [doi: 10.1016/j.vaccine.2012.04083].
- La Torre G, Saulle R, Unim B, Meggiolaro A, Barbato A, Mannocci A, et al. The effectiveness of measles-mumps-rubella (MMR) vaccination in the prevention of pediatric hospitalizations for targeted and untargeted infections: a retrospective cohort study. Hum Vaccin Immunother. 2017;13(8):1879–83.
- Livingston KA, Rosen JB, Zucker JR, Zimmerman CM. Mumps vaccine effectiveness and risk factors for disease in household during an outbreak in New York City. Vaccine. 2013;32(3):369–74 [doi: 10.1016/j.vaccine.2013.11.021].
- Ma C, Liu Y, Tang J, Jia H, Qin W, Su Y, et al. Assessment of mumps-containing vaccine effectiveness during an outbreak: importance to introduce the 2-dose schedule for China. Hum Vaccin Immunother. 2018;14(6):1392–7.
- Snijders BEP, van Lier A, van de Kassteele J, Fanoy EB, Ruijs WLM, Hulsof F, et al. Mumps vaccine effectiveness in primary schools and household, the Netherlands, 2008. Vaccine. 2012;30(19):2999–3002.

- Takla A, Bohmer MM, Klinc C, Kurz N, Schaffer A, Stich H, et al. Outbreak-related mumps vaccine effectiveness among a cohort of children and of young adults in Germany 2011. Hum Vaccin Immunother. 2014;10(1):140–5.

Summary of findings relating to GRADE table 1: Efficacy of mumps-containing vaccines: Cohort studies – Jeryl–Lynn strain, 1 dose	
Statement on quality of evidence	Low = Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 2, or ⊕⊕).
Conclusion	The level of certainty of evidence is graded as “low” due to serious inconsistency and the limited number of studies available. However, all studies indicate that mumps-containing vaccines prevent mumps disease.

Annex 2. GRADE table: Efficacy of mumps-containing vaccines: Cohort studies – Jeryl–Lynn strain, 2 doses

Population: Children aged 0–15 years

Intervention: 2 doses of mumps-containing vaccines with Jeryl–Lynn strain

Comparison: No vaccination/unvaccinated

Outcomes: Clinical and laboratory-confirmed mumps disease

Question: Should vaccination with 2 doses of mumps-containing vaccine with the Jeryl–Lynn strain, vs no vaccination, be used for the prevention of mumps disease?

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mumps vaccine**	**Unvaccinated**	**Relative (95% CI)**	**Absolute**	**Quality of evidence**
5	Observational studies[a]	No serious risk of bias	Serious inconsistency[b]	No serious indirectness	No serious imprecision	Large sample size[c]	124/5097	103/2695	RR: 0.14 (0.07–0.27)	–	⊕⊕◯◯ LOW[d]

CI = confidence interval; RR = relative risk.

[a] Cohort studies: Jeryl–Lynn strain, 2 doses; [b] I^2 = 81%; [c] RR: 0.14 (0.07–0.27) with 7792 participants; [d] In the Cochrane review, the quality was graded "Moderate", but was downgraded here because of serious inconsistency and upgraded for low RR.

References

- Greenland K, Whelan J, Fanoy E, Borgert M, Hulshof K, Yap KB, et al. Mumps outbreak among vaccinated university students associated with a large party, the Netherlands 2010. Vaccine. 2012;30(31):4676–80 [doi: 10.1016/j.vaccine.2012.04083].
- La Torre G, Saulle R, Unim B, Meggiolaro A, Barbato A, Mannocci A, et al. The effectiveness of measles-mumps-rubella (MMR) vaccination in the prevention of pediatric hospitalizations for targeted and untargeted infections: a retrospective cohort study. Hum Vaccin Immunother. 2017;13(8):1879–83.
- Livingston KA, Rosen JB, Zucker JR, Zimmerman CM. Mumps vaccine effectiveness and risk factors for disease in household during an outbreak in New York City. Vaccine. 2013;32(3):369–74 [doi: 10.1016/j.vaccine.2013.11.021].
- Snijders BEP, van Lier A, van de Kassteele J, Fanoy EB, Ruijs WLM, Hulsof F, et al. Mumps vaccine effectiveness in primary schools and household, the Netherlands, 2008. Vaccine. 2012;30(19):2999–3002.
- Takla A, Bohmer MM, Klinc C, Kurz N, Schaffer A, Stich H, et al. Outbreak-related mumps vaccine effectiveness among a cohort of children and of young adults in Germany 2011. Hum Vacc Immunother. 2014;10(1):140–5.

Summary of findings relating to GRADE table 2: Efficacy of mumps-containing vaccines: Cohort studies – Jeryl–Lynn strain, 2 doses	
Statement on quality of evidence	Low = Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 2, or ⊕⊕).
Conclusion	The level of certainty of evidence is graded as “low” due to serious inconsistency and the limited number of studies available. However, all studies indicate that mumps-containing vaccines prevent mumps disease.

Annex 3. GRADE table: Efficacy of mumps-containing vaccines: Cohort studies – Jeryl–Lynn strain, unspecified number of doses

Population: Children aged 0–15 years

Intervention: Mumps-containing vaccines with Jeryl–Lynn strain, unspecified number of doses

Comparison: No vaccination/unvaccinated

Outcomes: Clinical and laboratory-confirmed mumps disease

Question: Irrespective of number of doses, should vaccination with mumps-containing vaccine with the Jeryl–Lynn strain, vs no vaccination, be used for the prevention of mumps disease?

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mumps vaccine**	**Unvaccinated**	**Relative (95% CI)**	**Absolute**	**Quality of evidence**
4	Observational studies[a]	Serious risk of bias[b]	No serious inconsistency[c]	Serious indirectness	No serious imprecision	None	34/1297	69/714	RR: 0.23 (0.14–0.35)	–	⨁◯◯◯ VERY LOW[d]

CI = confidence interval; RR = relative risk.

[a] Cohort studies: Jeryl–Lynn strain, unspecified number of doses; [b] All the selected studies had unclear risk of bias; [c] $I^2 = 0\%$; [d] In the Cochrane review, the quality was graded "Low", but was downgraded here because of serious risk of bias.

References

- Chamot E, Toscani L, Egger P, Germann D, Bourquin C. Estimation of the efficacy of three strains of mumps vaccines during an epidemic of mumps in the Geneva canton (Switzerland). Rev Epidemiol Sante Publique. 1998;46(2):100–7.
- Livingston KA, Rosen JB, Zucker JR, Zimmerman CM. Mumps vaccine effectiveness and risk factors for disease in household during an outbreak in New York City. Vaccine. 2013;32(3):369–74 [doi: 10.1016/j.vaccine.2013.11.021].
- Ong G, Goh KT, Ma S, Chew SK. Comparative efficacy of Rubini, Jeryl-Lynn and Urabe mumps vaccine in an Asian population. J Infect. 2005;51(4):294–8.
- Schlegel M, Osterwalder JJ, Galeazzi RL, Vernazza PL. Comparative efficacy of three mumps vaccines during disease outbreak in Eastern Switzerland: cohort study. BMJ. 1999;319(7206):352.

Summary of findings relating to GRADE table 3: Efficacy of mumps-containing vaccines: Cohort studies – Jeryl–Lynn strain, unspecified number of doses	
Statement on quality of evidence	Very low = Evidence supports a very low level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 1, or ⊕)
Conclusion	The level of certainty of evidence is graded as “very low” due to serious risk of bias and the limited number of studies available. However, all studies indicate that mumps-containing vaccines prevent mumps disease.

Annex 4. GRADE table: Safety of mumps-containing vaccines: Encephalitis or encephalopathy: case–control MMR, risk interval 0–90 days

Population: Children aged 0–15 years

Intervention: Mumps-containing vaccines

Comparison: No vaccination/unvaccinated

Outcomes: Clinical and laboratory-confirmed mumps disease

Serious adverse events following immunization

Question: Can vaccination with mumps-containing vaccine, vs no vaccination, be used safely for the prevention of mumps disease?

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mumps vaccine**	**Unvaccinated**	**Relative (95% CI)**	**Absolute**	**Quality of evidence**
1	Observational study[a]	No serious risk of bias	Not applicable	No serious indirectness	No serious imprecision	Large sample size[b]	15/452	44/1280	OR: 0.98 (0.64–1.50)	–	⊕⊕⊕◯ MODERATE[c]

CI = confidence interval; OR = odds ratio.

[a] Encephalitis or encephalopathy: case–control MMR (risk interval 0–90 days); [b] Sample size: 2 197 000 children; [c] Confidence upgraded due to large sample size.

Reference

- Ray P, Hayward J, Michelson D, Lewis E, Schwalbe J, Black S, et al. Encephalopathy after whole-cell pertussis or measles vaccination: lack of evidence for a causal association in a retrospective case-control study. Pediatr Infect Dis J. 2006;25(9):768–73.

Summary of findings relating to GRADE table 4: Safety of mumps-containing vaccines: Encephalitis or encephalopathy: case–control MMR, risk interval 0–90 days	
Statement on quality of evidence	Moderate = Evidence supports a moderate level of confidence that the true effect lies close to that of the effect estimate of the health outcome (level 3, or ⊕⊕⊕)
Conclusion	Although studies giving strain-specific information are limited, the level of certainty of evidence is graded as “moderate” due to the large sample size.

Annex 5. GRADE table: Safety of mumps containing vaccines: Encephalitis or encephalopathy: person-time cohort – Jeryl–Lynn strain

Population: Children aged 0–15 years

Intervention: Mumps-containing vaccines with Jeryl–Lynn strain

Comparison: No vaccination/unvaccinated

Outcomes: Clinical and laboratory confirmed mumps disease

Serious adverse events following immunization

Question: Can vaccination with mumps-containing vaccine with the Jeryl–Lynn strain, vs no vaccination, be used safely for the prevention of mumps disease?

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mumps vaccine**	**Unvaccinated**	**Relative (95% CI)**	**Absolute**	**Quality of evidence**
1[a]	Observational study[b]	No serious risk of bias	Not applicable	No serious indirectness	No serious imprecision	Large sample size[c]	–	–	RR: 0.72 (0.36–1.43)	–	⊕⊕⊕◯ MODERATE[d]

CI = confidence interval; RR = relative risk.

[a] The Cochrane review included an additional study by Ward et al; this was removed here due to encephalitis not being a described outcome; [b] Encephalitis or encephalopathy: person-time cohort – Jeryl–Lynn; [c] Sample size: 535 544 children; [d] Confidence upgraded due to large sample size.

Reference

- Makela A, Nuorti JP, Peltola H. Neurologic disorders after measles-mumps-rubella vaccination. Pediatrics. 2002;110(5):957–63.

Summary of findings relating to GRADE table 5: Safety of mumps containing vaccines: Encephalitis or encephalopathy: person-time cohort – Jeryl–Lynn strain	
Statement on quality of evidence	Moderate = Evidence supports a moderate level of confidence that the true effect lies close to that of the effect estimate of the health outcome (level 3, or ⊕⊕⊕)
Conclusion	Although studies giving strain-specific information are limited, the level of certainty of evidence is graded as “moderate” due to the large sample size.

Annex 6. GRADE table: Safety of mumps-containing vaccines: Aseptic meningitis: case–control – Jeryl–Lynn strain, risk interval 0–30 days

Population: Children aged 0–15 years

Intervention: Mumps-containing vaccines with Jeryl–Lynn strain

Comparison: No vaccination/unvaccinated

Outcomes: Clinical and laboratory-confirmed mumps disease

Serious adverse events following immunization

Question: Can vaccination with mumps-containing vaccine with the Jeryl–Lynn strain, vs no vaccination, be used safely for the prevention of mumps disease?

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mumps vaccine**	**Unvaccinated**	**Relative (95% CI)**	**Absolute**	**Quality of evidence**
1	Observational study[a]	No serious risk of bias	Not applicable	No serious indirectness	No serious imprecision	Large sample size[b]	3/59	7/118	OR: 0.85 (0.21–3.41)	–	⊕⊕⊕◯ MODERATE[c]

CI = confidence interval; OR = odds ratio.

[a] Aseptic meningitis: case–control – Jeryl–Lynn strain (risk interval 0–30 days); [b] Sample size: 500 000 children; [c] Confidence upgraded due to large sample size.

Reference

- Black C, Kaye JA, Jick H. MMR vaccine and idiopathic thrombocytopaenic purpura. Br J Clin Pharmacol. 2003;55(1):107–11.

Summary of findings relating to GRADE table 6: Safety of mumps-containing vaccines: Aseptic meningitis: case–control – Jeryl–Lynn strain, risk interval 0–30 days	
Statement on quality of evidence	Moderate = Evidence supports a moderate level of confidence that the true effect lies close to that of the effect estimate of the health outcome (level 3, or ⊕⊕⊕)
Conclusion	Although studies giving strain-specific information are limited, the level of certainty of evidence is graded as “moderate” due to the large sample size.

Annex 7. GRADE table: Safety of mumps-containing vaccines: Aseptic meningitis: self-controlled case series – Leningrad–Zagreb strain

Population: Children aged 0–15 years

Intervention: Mumps-containing vaccines with Leningrad–Zagreb strain

Comparison: No vaccination/unvaccinated

Outcomes: Clinical and laboratory-confirmed mumps disease

Serious adverse events following immunization

Question: Can vaccination with mumps-containing vaccines with the Leningrad–Zagreb strain, vs no vaccination, be used safely for the prevention of mumps disease?

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency (heterogeneity)**	**Indirectness**	**Imprecision**	**Other considerations**	**Mumps vaccine**	**Unvaccinated**	**Relative (95% CI)**	**Absolute**	**Quality of evidence**
1	Observational study[a]	Serious risk of bias[b]	Not applicable	No serious indirectness	Serious imprecision[c]	None	–	–	OR: 6.40 (0.3–124.4)[d]	–	⨁◯◯◯ VERY LOW

CI = confidence interval; RR = relative risk.

[a] Aseptic meningitis: self-controlled case series, Leningrad–Zagreb strain; [b] Serious risk of bias because the study was not primarily set up to evaluate the association between MMR and aseptic meningitis; [c] Serious imprecision due to wide confidence interval; [d] Adjusted odds ratio as presented by the original paper by Perez-Vilar et al.

Reference

- Perez-Vilar S, Weibel D, Sturkenboom M, Black S, Maure C, Castro JL, et al. Enhancing global vaccine pharmacovigilance: proof-of-concept study on aseptic meningitis and immune thrombocytopenic purpura following measles-mumps containing vaccination. Vaccine. 2018;36(3):347–54.

Summary of findings relating to GRADE table 7: Safety of mumps-containing vaccines: Aseptic meningitis: self-controlled case series – Leningrad–Zagreb strain	
Statement on quality of evidence	Very low = Evidence supports a very low level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 1, or ⊕)
Conclusion	The level of certainty of evidence is graded as “very low” due to serious risk of bias and the limited number of studies available.

Annex 8. GRADE table: Safety of mumps-containing vaccines: Aseptic meningitis: person-time cohort – Jeryl–Lynn strain

Population: Children aged 0–15 years

Intervention: Mumps-containing vaccines with Jeryl–Lynn strain

Comparison: No vaccination/unvaccinated

Outcomes: Clinical and laboratory-confirmed mumps disease

Serious adverse events following immunization

Question: Can vaccination with mumps-containing vaccines with the Jeryl–Lynn strain, vs no vaccination, be used safely for the prevention of mumps disease?

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mumps vaccine**	**Unvaccinated**	**Relative (95% CI)**	**Absolute**	**Quality of evidence**
1	Observational study[a]	No serious risk of bias	Not applicable	No serious indirectness	No serious imprecision	Large sample size[b]	–	–	RR: 1.30 (0.66–2.56)	–	⨁⨁⨁◯ MODERATE[c]

CI = confidence interval; RR = relative risk.

[a] Aseptic meningitis: person-time cohort – Jeryl–Lynn strain; [b]Sample size: 535 544 children; c Confidence upgraded due to large sample size.

Reference

- Makela A, Nuorti JP, Peltola H. Neurologic disorders after measles-mumps-rubella vaccination. Pediatrics. 2002;110(5):957–63.

Summary of findings relating to GRADE table 8: Safety of mumps-containing vaccines: Aseptic meningitis: person-time cohort – Jeryl–Lynn strain	
Statement on quality of evidence	Moderate = Evidence supports a moderate level of confidence that the true effect lies close to that of the effect estimate of the health outcome (level 3, or ⊕⊕⊕)
Conclusion	Although studies giving strain-specific information are limited, the level of certainty of evidence is graded as “moderate” due to the large sample size.

Annex 9. GRADE table: Safety of mumps-containing vaccines. Aseptic meningitis: case only, ecological method – Leningrad–Zagreb strain

Population: Children aged 0–15 years

Intervention: Mumps-containing vaccines with Leningrad–Zagreb strain

Comparison: No vaccination

Outcomes: Clinical and laboratory-confirmed mumps disease

Serious adverse events following immunization

Question: Can vaccination with mumps-containing vaccines with the Leningrad–Zagreb strain, vs no vaccination, be used safely for the prevention of mumps disease?

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mumps vaccine**	**Unvaccinated**	**Relative (95% CI)**	**Absolute**	**Quality of evidence**
3[a]	Observational studies[b]	No serious risk of bias	No serious inconsistency[c]	No serious indirectness	No serious imprecision	Large sample size[d]	–	–	RR: 18.56 (12.09–28.51)	–	⊕⊕◯◯ LOW

CI = confidence interval; RR = relative risk.

[a] Two studies, with three different arms; [b] Aseptic meningitis: case only, ecological method – Leningrad–Zagreb strain; [c] I^2 = 32%; [d] Sample size: 1 164 934 children

References

- da Cunha SS, Rodrigues LC, Barreto ML, Dourado I. Outbreak of aseptic meningitis and mumps after mass vaccination with MMR vaccine using the Leningrad-Zagreb mumps strain. Vaccine. 2002;20(7-8):1106–12.
- da Silveira CM, Kmetzsch CI, Mohrdieck R, Sperb AF, Prevots DR. The risk of aseptic meningitis associated with the Leningrad-Zagreb mumps vaccine strain following mass vaccination with measles-mumps-rubella vaccine, Rio Grande do Sul, Brazil, 1997. Int J Epidemiol. 2002;31(5):978–82.

Summary of findings relating to GRADE table 9: Safety of mumps-containing vaccines. Aseptic meningitis: case only, ecological method – Leningrad–Zagreb strain	
Statement on quality of evidence	Low = Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 2, or ⊕⊕).
Conclusion	The level of certainty of evidence is graded as "low" due to serious inconsistency and the limited number of studies available. However, all studies indicate that mumps-containing vaccines prevent mumps disease.

Annex 10. SAGE Evidence-to-decision framework

Question:	Should vaccination with mumps-containing vaccine, vs no vaccination, be used to prevent mumps disease?
Population:	Children aged 0–15 years
Intervention:	Vaccination with mumps-containing vaccines
Comparison(s)	No vaccination
Outcome:	Mumps disease (clinical or laboratory-confirmed)

Background:

Humans are the only known natural host for mumps virus and the only source of transmission. A member of the Paramyxoviridae family, mumps virus is spread via direct contact or by air-borne droplets from the upper respiratory tract of infected individuals. The incubation time averages 16–18 days with a range of 12–25 days *(2)*.

With no specific therapy, mumps (parotitis epidemica) is an acute viral illness characterized by unilateral or bilateral tenderness or inflammatory swelling of the parotid or other salivary glands (parotiditis) *(3)*. Although mostly a mild childhood disease, frequently reported in children aged 5–9 years, cases of mumps infection among adolescents and adults have been reported, and are associated with higher rates of complications, including orchitis, oophoritis, mastitis, meningitis, encephalitis, pancreatitis and hearing loss *(4–6)*. Mumps is prevented through vaccination. The development and commercialization of safe, live attenuated mumps vaccines in the late 1960s, led to a considerable reduction in incidence of mumps – from about 100–1 000 cases per 100 000 population to <1 case per 100 000 population *(7)*.

By the end of 2023, only 123 (63%) of 194 WHO Member States had introduced at least 1 dose of mumps-containing vaccine (monovalent mumps vaccine, MMR and MMRV) (See: WHO Immunization Data portal).

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE and ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	**Uncertain and varies by setting**	**Uncertain:** Although endemic globally, mumps is not considered a significant public health problem when compared to other vaccine-preventable diseases, such as measles. Global incidence of mumps is difficult to ascertain as mumps is not a notifiable disease in many countries. Furthermore, there is poor documentation of clinical cases and a lack of published studies especially in low- and middle-income countries (LMICs). The number of mumps cases, when reported, may be underestimated as many unvaccinated and vaccinated individuals remain asymptomatic and do not seek health-care services. Data from the WHO/UNICEF Joint Reporting Form show an increase in the number of mumps cases reported, with the caveat that data are self-reported by countries, and not always complete. Epidemiological data are often obtained from investigations of mumps outbreaks and from the pre-vaccination era. Before the 1960s, when mumps vaccines became commercially available, mumps was a common infectious disease in all parts of the world, with annual incidences ranging from 100 to 1 000 cases per 100 000 population. **Depending on the setting**, mumps could be considered a public health priority. During the past decades, mumps outbreaks among young adults have been reported among vaccinated individuals in close and frequent contact, for example in settings such as universities and military barracks. As with rubella, insufficient coverage of childhood vaccination can result in an epidemiological shift in incidence of mumps to older age groups, potentially leading to a more serious disease burden – for example due to orchitis, aseptic meningitis and encephalitis – than had occurred before vaccination introduction. In the pre-vaccine era, orchitis occurred in up to a third of mumps cases in post-pubertal males, while the estimated frequencies for aseptic meningitis and encephalitis among unvaccinated mumps patients were <1–10% and ≤1%, respectively. Although a rare event, encephalitis, a more serious infection, can develop after mumps infection and is responsible for most fatal cases. With mumps vaccination, the estimated frequencies for orchitis, aseptic meningitis and encephalitis were 6%, ≤1% and ≤1%, respectively *(8–11)*.

BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	**Yes**	In countries where large-scale vaccination programmes against mumps have been implemented, disease incidence has dropped dramatically since 1967, from about 100–1 000 cases per 100 000 population to <1 case per 100 000 population *(4)*. Data prior to the introduction of mumps vaccines show that the burden of mumps disease was staggering when considering the direct costs for outpatient and inpatient visits, costs of outbreak control, and productivity losses incurred by days of missed work, including for the provision of care for sick children and family members. Except for the Rubini strain, all vaccine strains of the mumps virus have been demonstrated to achieve vaccine effectiveness following 1 and 2 doses, although estimates range widely across studies *(11)*. Investigations of multiple outbreaks in highly-vaccinated populations have shown the ability of the current mumps vaccines to attenuate the severity of symptoms and complications. Individuals who received 2-dose vaccination were less likely to be hospitalized or affected by severe mumps complications (e.g. orchitis, meningitis, or encephalitis) than those who were vaccinated with 1 dose or unvaccinated.

	Harms of the intervention Are the undesirable anticipated effects small?	**Yes, with gradual differences between vaccine products**	Adverse events following immunization (AEFIs) Vaccination with mumps-containing vaccines can have rare AEFIs depending on the strain used in the vaccine. However, the undesirable anticipated effects are small. Studies in Croatia of mumps-containing vaccines with the Leningrad–Zagreb strain showed vaccine efficacy of 97–100% in field trials *(12)*. This strain has been associated with an increased risk of aseptic meningitis *(13, 14)* although incidence at ≤1% *(15, 16)* is lower than aseptic meningitis caused by mumps infection (<1–10%) *(9, 10)*. The difference in frequency of vaccine-associated aseptic meningitis reflects not only differences in the propensity of vaccines, including different viral strains in causation, but also a lack of a consensual definition of post-vaccine aseptic meningitis, related to variation in study design and diagnostic criteria *(17, 18)*. Despite the occurrence of these cases, the perceived risk–benefit ratio of use of the Leningrad–Zagreb mumps vaccines over several years in routine programmes in developing countries is considered acceptable. However, if mumps vaccine strains that have been associated with an increased risk of aseptic meningitis are to be used in mass campaigns, vaccination programmes should implement appropriate strategies for communicating risk and managing cases in order to handle possible reports of clusters of aseptic meningitis *(19)*. Low vaccination coverage The aim of including mumps vaccination as part of a national immunization programme should be to achieve an elevated level of disease control, As seen with rubella, insufficient childhood vaccination coverage against mumps can result in an epidemiological shift of disease incidence to older age groups, potentially leading to higher rates of serious disease and complications than had occurred before the introduction of large-scale vaccination. Coverage rates below 70–80% may result in an epidemiological shift, as reduced (but not interrupted) circulation of mumps virus in the community may result in an increased number of cases in adults without immunity from natural infection and at greater risk for complications.

	What is the balance between benefits and harms?	**Favours intervention**	Effectiveness and seroprevalence data demonstrate that mumps-containing vaccines are efficacious and provide protection against mumps disease. The use of mumps-containing vaccines in routine vaccination programmes has resulted in significant reductions globally in mumps incidence – from about 100–1000 cases per 100 000 population to <1 case per 100 000 population *(7)*. The burden of mumps disease without vaccination is staggering in terms of: i) direct costs for treatment and complications during health-care outpatient and inpatient visits; ii) costs of outbreak control; iii) indirect costs, such as productivity losses incurred by days of missed work, including the provision of care for sick children or patients themselves *(20, 21)*. In highly-vaccinated populations, recent outbreaks of mumps have occurred in 2-dose recipients (mostly adolescents and young adults), although the total number of mumps cases has never reached pre-vaccination levels *(22)*. However, those who received 2-dose vaccination were less likely to be hospitalized or affected by severe mumps complications (orchitis, meningitis, or encephalitis) than those who were vaccinated with 1 dose or unvaccinated *(9, 23)*. Further research is needed to explain the resurgence of mumps cases in countries with high MMR coverage.
	What is the overall quality of this evidence for the critical outcomes?	**Quality of evidence varies for efficacy and safety**	The quality of the evidence for efficacy and safety is graded "Very low" to "Moderate" due to the limited numbers of studies (see GRADE above).
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes (related to disease, not vaccine)?	**Probably no important uncertainty or variability**	Global mumps incidence is difficult to ascertain as mumps is not a notifiable disease in many countries. There is poor documentation of clinical cases and a lack of published studies, especially in LMICs. The number of mumps cases, when reported, may be underestimated as many unvaccinated and vaccinated individuals remain asymptomatic and do not seek health-care services. Data pre-introduction of mumps vaccines show that the burden of mumps disease was staggering when considering direct costs for outpatient and inpatient visits, costs of outbreak control, and productivity losses incurred by days of missed work, including for provision of care for sick children and family members.

	<u>Values and preferences of the target population</u> Are the desirable effects large relative to the undesirable effects (of vaccines valued by population)?	**Yes**	In countries where large-scale vaccination against mumps has been implemented, disease incidence has dropped dramatically since 1967 *(4)*. Given the existing use of MMR vaccines globally, the benefits of ensuring vaccination against mumps in addition to rubella and measles would be a plausible public health intervention that could yield significant clinical and economic benefits. It would ensure vaccination against mumps in addition to greater vaccination rates against measles and rubella.
RESOURCE USE	Are the resources required small?	**Varies**	In most countries, vaccination against mumps is delivered via a combined measles–mumps–rubella (MMR) vaccine. The infrastructure for vaccination with MMR already exists. By the end of 2022, all 194 (100%) WHO Member States had introduced at least 1 dose of measles-containing vaccine (MCV), and 179 (92%) countries had introduced at least 1 dose of rubella-containing vaccine (RCV), as measles–rubella (MR) vaccine. The resources required to support the switch from MR to MMR depends primarily on vaccine costs, especially for lower-middle-income and middle-income countries. In 2018, the reported price per dose for MMR vaccines was US$ 1.08–123.40 vs US$ 0.55–10.30 for MR vaccines. Compared to a price of US$ 1.10 for 10 doses of MR, the reported median price for the single-dose vial of MMR by self-procuring middle-income countries was nearly six times higher *(24)*.

	Is the intervention cost–effective?	**Varies**	The cost difference between MR and MMR vaccines is a critical issue for countries when considering country context and the cost–effectiveness of substituting MMR for MR vaccines in their national immunization programmes. The cost–effectiveness of MMR vs MR vaccines is impacted by country-specific considerations including coverage of MR, the price differential between MR and MMR, and the disease burden of mumps, which in turn relates to the impact on the health-care system of mumps outbreaks and the clinical management of complications. The incremental cost–effectiveness of mumps-containing vaccine based on actual or estimated reduction of morbidity, mortality and associated health-care costs was highly favourable in the high-income settings of the United States and Japan *(25–27)*. From the perspectives of both taxpayer and society, Oh et al estimated that the benefits of a routine 2-dose MMR vaccination programme with Leningrad–Zagreb mumps strain in Fiji outweighed the costs associated with such a programme *(21)*.
EQUITY	What would be the impact on health inequities?	**Reduced**	The introduction of MMR vaccines into successful (i.e. with high MMR coverage) national immunization programmes led to dramatic reductions in the incidence of mumps¸ measles and rubella.
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	**Intervention**	By the end of 2023, 123 (63%) of 194 WHO Members States had introduced mumps vaccination into their routine schedule, often in combination with measles and rubella vaccines (MMR or MMRV). Lessons learned from countries that have included mumps vaccination into their routine programmes are: the need of evidence of vaccine efficacy, safety and economic benefits; collaboration between governments and United Nations agencies (particularly, the United Nations' Children's Fund); strong political will for incorporating mumps into the current vaccination programme; and awareness raising for MMR vaccination in the population *(21)*
	Which option is acceptable to the target group?	**Intervention**	In 1993, MMR was withdrawn from the Japanese National Immunization Program due to a high incidence of aseptic meningitis following vaccination. Mumps vaccination was then classified as voluntary. Results of a parent survey conducted between October 2019 and February 2020 show that concern about aseptic meningitis after vaccination against mumps was not the current obstacle to vaccination. To further promote vaccination against mumps, it was necessary to improve the knowledge of parents on vaccination in general as well as to provide information on mumps and mumps vaccines, their benefits and risks *(28)*.

FEASIBILITY	Is the intervention feasible to implement?	**Yes**	In most countries, vaccination against mumps is delivered via a combined measles–mumps–rubella (MMR) vaccine. By the end of 2023, all 194 (100%) WHO Member States had introduced at least 1 dose of measles-containing vaccine (MCV). The infrastructure for vaccination with MMR already exists. For countries considering the introduction of MMR, public health experts should consider costs of implementation including vaccine procurement; surveillance to monitor disease incidence and AEFIs; health-care worker training and public communication; and health-care savings since incidence of mumps and its complications will be considerably reduced.
BALANCE OF CONSEQUENCES		**Desirable consequences *clearly outweigh* undesirable consequences in most settings**	
TYPE OF RECOMMENDATION		**We recommend the intervention of vaccination with mumps-containing vaccines**	
RECOMMENDATION (TEXT)		**Please refer to the WHO 2024 Mumps vaccines position paper**	
IMPLEMENTATION CONSIDERATIONS		**Please refer to the WHO 2024 Mumps vaccines position paper**	
MONITORING, EVALUATION AND RESEARCH PRIORITIES		**Please refer to the WHO 2024 Mumps vaccines position paper**	

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