Strategic Advisory Group of Experts (SAGE) on Immunization Evidence to recommendations framework[i]

Question: Should varicella (-containing) vaccine be recommended over no vaccination in immunocompetent children (≥9 months of age) to prevent varicella disease?
Population: Immunocompetent children (≥9 months of age)
Intervention: Vaccination with varicella vaccine (monovalent varicella vaccine or tetravalent vaccine containing measles, rubella, mumps and varicella strains (MMRV))
Comparison(s): Placebo/no vaccination
Outcome: Clinical or laboratory-confirmed varicella disease (all grades of severity)

Background: Endemic worldwide, varicella-zoster virus (VZV) is a highly contagious herpes virus which causes both varicella (chickenpox) and herpes zoster (shingles). The estimated global burden of morbidity and mortality caused by varicella is considerably lower than that due to other major childhood infectious diseases such as measles or pertussis. Based on the 2021 Institute for Health Metrics and Evaluation (IHME) data on varicella, the number of varicella-related global deaths across all age groups was 13,930.70 (95%CI: 12,584.93-15,604.98) and a global incidence of 86,678,086.71 (95%CI: 81,687,120.87- 92,207,569.31).

In pre-vaccination era, varicella incidence ranged from 320 to 1600 cases per 100,000 with case-fatality of approximately 3 per 100,000 cases. Although varicella vaccines are licensed worldwide, few countries have introduced varicella vaccination in their national immunization programme. Introduction of varicella vaccination led to significant decrease in incidence with no evidence of a shift of varicella disease burden to older age groups.

In 2014, WHO issued the varicella and herpes zoster vaccines position paper. It included the following recommendation on the use of varicella (-containing) vaccines: Countries where varicella is an important public health burden could consider introducing varicella vaccination in the routine childhood immunization programme.

In 2024, WHO established a technical consultation to revisit the evidence and propose updated recommendations on the use of varicella vaccination.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Un-certain*	*Yes*	*Varies by setting*	Varicella is a highly communicable, self-limited illness. Disease is characteristically not severe, although there are associated complications. These include bacterial superinfections (such as cellulitis, pneumonia, osteomyelitis), and neurological complications (such as cerebellar ataxia, encephalitis). In rare instances, such complications may lead to long-term sequelae or death.[1],[2] Complications from varicella occur more frequently in persons older than 15 years old.[3] From 1990 to 2019, the estimated global numbers of incident and death cases due to varicella were 83 963 744 and 14 553.[4]	
		☐	☐	☒	☐		
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention	*No*	*Un-certain*	*Yes*	*Varies*	Immunization is the most effective preventive strategy against varicella. Before the introduction of	

	Are the desirable anticipated effects large?	☐	☐	☒	☐	routine vaccination, varicella contributed significantly to the burden of childhood disease.[5] Comparing pre (1993–1995) and post-vaccination (1996–2004), varicella-related ambulatory visits were reduced by 66% ($p < 0.001$), reaching 98% of reduction in children younger than 4 years of age in United States[6] by more than 90%[7]. Similar results have been reported in numerous countries which have introduced varicella vaccination in their national programmes.[8], [9],[10],[11],[12],[13]	
	Harms of the intervention Are the undesirable	*No*	*Un-certain*	*Yes*	*Varies*	On the individual basis, monovalent varicella vaccine was well tolerated during pre-licensure clinical trials. This was confirmed by	

	anticipated effects small?	☐	☐	☒	☐	post-licensure data. Some very serious adverse events following immunization include an increased risk of severe rash, lung or liver infections, meningitis and febrile seizures following varicella vaccination.[14] A review of post-licensure safety studies of the combination measles, mumps, rubella (MMR) and varicella vaccine, which contains the Oka strain identified a risk of febrile seizures after vaccination among children aged 12–23 months, compared with children receiving separate MMR and varicella vaccination.[15] On a population basis, an assumed undesired effect of a routine varicella vaccine program in children may be increased morbidity and mortality due to a shift of varicella infection to a higher age group if high vaccination coverage cannot be achieved. This has not been confirmed in countries	

							using varicella vaccination in their national programme. Further, re-exposure to circulating varicella disease can inhibit varicella reactivation and consequently also decrease the incidence of herpes zoster in immune individuals. Decrease of varicella circulation due to childhood varicella immunization programs may temporarily increase the incidence of herpes zoster.	
	Balance between benefits and harms	Favours inter-vention	Favours com-parison	Favours both	Favours neither	Unclear	On an individual level, serious adverse events following immunization are rare and the vaccine provides high, long-lasting protection against varicella. Modeling indicated that for countries, at vaccine coverage levels of <30% and ≥80% very little risk exists of increased morbidity due to shifts in the age of infection. However, at moderate coverage levels (30%-70%), there may be a	
		☒	☐	☐	☐	☐		

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<tr><td rowspan="4"></td><td rowspan="4">What is the overall quality of this evidence for the critical outcomes?</td><td colspan="5">Efficacy/effectiveness of the intervention</td><td rowspan="4">On efficacy /effectiveness, and safety of MMR vs MMRV see Cochrane review[16] and related GRADE tables.

No new systematic review on the safety of varicella vaccines was conducted. Based on a 2013 systematic review, the certainty of evidence on the safety of varicella vaccines was moderate.[17]</td><td rowspan="4"></td></tr>
<tr><td>No included studies</td><td>Very low</td><td>Low</td><td>Mod-erate</td><td>High</td></tr>
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<tr><td colspan="5">Safety of the intervention

No included studies | Very low | Low | Mod-erate | High
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<tr><td>VALUES & PREFERENCES</td><td>How certain is the relative importance of the desirable and undesirable outcomes?</td><td>Important uncertainty or variability</td><td>Possibly important uncertainty or variability</td><td>Probably no important uncertainty or variability</td><td>No important uncertainty or variability</td><td>No known undesirable outcomes</td><td>No global evidence could be retrieved on the relative importance of desirable and undesirable effects following infection (disease, severe disease, immunity against varicella, reactivation of latent disease), but it is assumed that different target populations value the outcome differently.</td><td></td></tr>
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	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No*	*Probably No*	*Uncertain*	*Probably Yes*	*Yes*	*Varies*	No global evidence could be retrieved on the global values and preferences of the target population, but it would be assumed that at the individual level, avoidance of varicella related disease would outweigh the undesirable effects related to immunization (pain during immunization, AEFIs). Herd protection would further reduce the risk of those who cannot receive the intervention.	
		☐	☐	☐	☒	☐	☐		

RESOURCE USE	Are the resources required small?	*No*	*Un-certain*	*Yes*	*Varies*	Varicella vaccines are available either as monovalent or as quadrivalent (MMRV). Data related to varicella vaccination are mostly from high income countries. Costs of the vaccine might impact implementation of varicella vaccination in low- and middle-income countries. Resources would need to be invested to reach high vaccination coverage to prevent a shift of varicella incidence to older age-groups.[18] Existing vaccination contacts for measles-containing vaccine could be used to administer varicella vaccines.	
		☐	☐	☐	☒		
	Cost-effectiveness	*No*	*Un-certain*	*Yes*	*Varies*	Mathematical modelling of varicella vaccination report substantial reduction in clinical and economic burden of varicella disease.[19],[20] Over recent years, economic evaluations of	
		☐	☐	☐	☒		

						varicella vaccination have been published, mostly for routine childhood programmes. [21],[22],[23],[24] A recent systematic literature review assessing the economic effectiveness of a variety of varicella vaccination programmes mostly in high- and middle-income countries suggests that the benefit of a universal childhood varicella vaccination programme depends on the disease burden as well as cost associated with treatment.[25] Few data are available for low-income countries.	
EQUITY	What would be the impact on health inequities?	*Increa-sed*	*Un-certain*	*Reduced*	*Varies*	Compared to temperate climate, in tropical climate the majority of studies have described later acquisition of varicella in childhood with a higher proportion of cases and higher susceptibility among adults. These features lead to a	
		☐	☐	☒	☐		

							higher overall mean age at varicella infection compared with temperate climates and associated higher morbidity. Further, treatment options may be reduced or non-existent in low-income settings.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention*	*Comparison*	*Both*	*Neither*	*Un-clear*	Countries should assess whether adequate resources can be allocated to implement and sustain varicella vaccination in the routine immunization schedule. This especially applies to low- and middle-income countries with limited resources, where varicella vaccination might be competing with other important public health interventions. Therefore, dependent on setting, the intervention or the comparison may be acceptable to key stakeholders.	
		☐	☐	☒	☐	☐		

FEASIBILITY	Which option is acceptable to target group?	*Inter-vention*	*Comparison*	*Both*	*Neither*	*Un-clear*				It is presumed that the intervention option would be acceptable to the target group if no additional visit to the health clinic is needed, and the costs are covered by the health care provider.	
		☐	☐	☒	☐	☐					
	Is the intervention feasible to implement?	*No*	*Probably No*	*Un-certain*	*Probably Yes*	*Yes*	*Varies*			Feasibility to implement may vary by setting. Due to the financial implications, the intervention may be more feasible to implement in high income countries rather than to middle and lower income countries.	
		☐	☐	☐	☐	☐	☒				
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	
		☐		☐				☐	☐	☒	

Type of recommendation	We recommend the intervention	We suggest considering recommendation of the intervention	We recommend the comparison	We recommend against the intervention and the comparison
	☐	☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☒ Only in specific contexts or specific (sub)populations	☐	☐
Recommendation (text)	See recommendations in the 2025 WHO vaccine position paper on varicella vaccines.			
Implementation considerations	See recommendations in the 2025 WHO vaccine position paper on varicella vaccines.			
Monitoring and evaluation	See recommendations in the 2025 WHO vaccine position paper on varicella vaccines.			
Research priorities	See recommendations in the 2025 WHO vaccine position paper on varicella vaccines.			

References

[1] Heininger U, Seward JF. Varicella. Lancet. 2006;368(9544):1365–76.

[2] European Centre for Disease Prevention and Control. Varicella vaccination in the European Union. Stockholm: ECDC; 2015. Varicella-Guidance-2015.pdf

[3] Gershon, A., Breuer, J., Cohen, J. et al. Varicella zoster virus infection. Nat Rev Dis Primers 1, 15016 (2015)

[4] Huang J, Wu Y, Wang M, et al. The global disease burden of varicella-zoster virus infection from 1990 to 2019. J Med Virol. 2022; 94: 2736-2746.

[5] Hammes Varela, F., Pinto, L. A., & Scotta, M. C. (2018). Global impact of varicella vaccination programs. Human Vaccines & Immunotherapeutics, 15(3), 645–657.

[6] Shah SS, Wood SM, Luan X, Ratner AJ. Decline in Varicella-related ambulatory visits and hospitalizations in the United States since routine immunization against Varicella. Pediatr Infect Dis J. 2010 Mar;29(3):199–204.

[7] Bialek SR, Perella D, Zhang J, Mascola L, Viner K, Jackson C, Lopez AS, Watson B, Civen R. Impact of a routine two-dose varicella vaccination program on Varicella epidemiology. Pediatrics. 2013 Nov 1;132(5):e1134–40..

[8] Rieck T, Feig M, An der Heiden M, Siedler A, Wichmann O. Assessing varicella vaccine effectiveness and its influencing factors using health insurance claims data, Germany, 2006 to 2015. Euro Surveill. 2017;22(17):pii=30521.

[9] Amodio E, Tramuto F, Cracchiolo M, Sciuto V, De Donno A, Guido M, Rota MC, Gabutti G, Vitale F. The impact of ten years of infant universal varicella vaccination in Sicily, Italy (2003–2012). Hum Vaccines Immunother. 2015 Jan;11(1):236–239.

[10] Elbaz M, Paret G, Yohai AB, Halutz O, Grisaru-Soen G. Immunisation led to a major reduction in paediatric patients hospitalised because of the varicella infection in Israel. Acta Paediatr. 2016 Apr;105(4):e161–6.

[11] Al-Turab M, Chehadeh W. Varicella infection in the Middle East: prevalence, complications, and vaccination. J Res Med Sci. 2018;23(1):19.

[12] Hattori F, Miura H, Sugata K, Yoshikawa A, Ihira M, Yahata Y, Kamiya H, Tanaka-Taya K, Yoshikawa T. Evaluating the effectiveness of the universal immunization program against varicella in Japanese children. Vaccine. 2017 Sep;35(37):4936–4941

[13] Dong, P., Wang, M., & Liu, Y. (2020). Epidemiological characteristics of varicella in China, 2016–2019. Chin J Vaccines Immun, 26(4), 403-406.

[14] Woodward M, Marko A, Galea S, Eagel B, Straus W. Varicella virus vaccine live: A 22-year review of postmarketing safety data. Open Forum Infect Dis 2019; 6:ofz295

[15] The WHO Global Advisory Committee on Vaccine Safety. Zoster vaccine safety and varicella vaccine safety in immunocompromised populations. Geneva. 2013 (Varicella Zoster virus, accessed 24 February 2025).

[16] Di Pietrantonj C, Rivetti A, Marchione P, Debalini MG, Demicheli V. Vaccines for measles, mumps, rubella, and varicella in children. Cochrane Database of Systematic Reviews 2020, Issue 4.

[17] Safety of varicella and MMRV vaccines: A systematic review. https://terrance.who.int/mediacentre/data/sage/SAGE_Docs_Ppt_Apr2014/6_session_varicella_herpes_zoster/Apr2014_session6_varicella_MMRV_safety.pdf, accessed 4 February 2025.

[18] Germinario C, Gallone MS, Cappelli MG, Tafuri S. Clinical benefits of routine varicella vaccination for adults. Hum Vaccin Immunother. 2015;11(6):1426-8.

[19] Burgess C, Samant S, leFevre T, Schade Larsen C, Pawaskar M. Universal varicella vaccination in Denmark: Modeling public health impact, age-shift, and cost-effectiveness. PLOS Glob Public Health. 2023 Apr 5;3(4):e0001743

[20] Hodgkinson B, Wang T, Byrnes J, Scuffham P. Modelling a cost-effective vaccination strategy for the prevention of varicella and herpes zoster infection: A systematic review. Vaccine. 2021 Mar 1;39(9):1370-1382.
[21] Thiry N, Beutels P, Van Damme P, et al. Economic evaluations of varicella vaccination programmes: a review of the literature. Pharmacoeconomics 2003; 21(1):13–38
[22] Rozenbaum MH, van Hoek AJ, Vegter S, et al. Cost-effectiveness of varicella vaccination programs: an update of the literature. Expert Rev Vaccines 2008; 7(6):753–782
[23] Unim B, Saulle R, Boccalini S, et al. Economic evaluation of varicella vaccination: results of a systemeatic review. Hum Vaccin Immunother 2013; 9(9):1932–1942
[24] Damm O, Ultsch B, Horn J, et al. Systematic review of models assessing the economic value of routine varicella and herpes zoster vaccination in high-income countries. BMC Public Health 2015; 15:533.
[25] Anderson R, Kim S, Roberts N, Petrou S. Systematic review of economic evaluations of varicella vaccination programmes. PLoS One. 2023 Mar 27;18(3):e0282327.

[i] This Evidence to Recommendation table is based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel). http://www.decide-collaboration.eu/WP5/Strategies/Framework