SAGE Evidence to recommendation framework[i]

Rubella vaccine PICO question 1:

Detailed documentation related to the evidence to recommendation table can be found in the background papers presented to the Strategic Advisory Group of Experts (SAGE) on Immunization in October 2019[1], in the SAGE meeting report[2] as well as in the related Rubella vaccine position paper.

Question: Which combined rubella and congenital rubella syndrome (CRS) control and elimination strategies should be recommended?

Population: Immunocompetent individuals
Intervention: Rubella vaccine as a part of routine immunization programmes, with additional activities as needed within a specific country context (i.e. Supplemental Immunization Activities (SIAs), catch ups and vaccination of women of reproductive age)
Comparison(s): Rubella vaccine only in women of reproductive age
Outcome: Cases of rubella and/or CRS

1 SAGE meeting of October 2019. Background documents. Summary of the systematic review and meta-analysis of the immunogenicity, duration of protection, effectiveness/efficacy and safety of rubella vaccine.
https://www.who.int/immunization/sage/meetings/2019/october/2_Systematic_review_of_rubella_vaccine_summary_yellow_book_final.pdf?ua=1, accessed July 2020
2 SAGE meeting report, October 2019. https://apps.who.int/iris/bitstream/handle/10665/329962/WER9447-eng-fre.pdf?ua=1, accessed July2020

Background:
Rubella vaccination is used primarily to prevent rubella infections in pregnancy and therefore prevent cases of CRS. In the past, CRS control was sought by using a strategy of vaccinating only women of reproductive age (WRA). Some countries have tried this CRS control strategy and found that large immunity gaps, particularly among adolescent and adult males, are created. These immunity gaps have resulted in large outbreaks in unprotected individuals, including pregnant women who have not been vaccinated and subsequently some infants are born with CRS. Additionally, goals for rubella have changed over time with a move towards both rubella and CRS elimination. The below evidence to recommendation table reviews the evidence used by the Measles and Rubella working group in their deliberations of the above policy question.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	The 2011 WHO position paper presented strategies for CRS control and Rubella Elimination. At that time, there were two approved strategies, i.e. countries could use CRS control strategies or Rubella elimination (preferred) strategies. A total of 26 006 cases of rubella and 449 cases of CRS were reported in 2018. These numbers are likely an underestimation of the true burden of disease, especially given the high percentage of asymptomatic or subclinical rubella.	Rubella vaccination programmes and Measles programmes are linked as most countries offer both antigens in a combination vaccine.
BENEFITS	Benefits of the intervention	*No*	*Un-certain*	*Yes*	*Varies*	Rubella vaccine in children demonstrates an effectiveness of 95% against rubella	Using a strategy that includes rubella vaccine in the routine

	Are the desirable anticipated effects large?	☐	☐	☒	infection. Since 2000, there has been a 97% decrease in the number of cases of rubella reported globally. Modelling indicated that the average incidence of CRS per 100 000 live births had decreased substantially between 1996 and 2010 in regions with high RCV coverage for example, from 56 (95% CI: 24,104) to <0.01 (95% CI: 0,1) per 100,000 in the Americas respectively.	programme, would allow for elimination of rubella infections and CRS.
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	Rubella vaccine has been used in routine childhood programmes for many years and has been shown to be safe, with few severe side effects in the population at large. Additional activities such as SIAs, catch up campaigns and vaccination of WRA can be part of a comprehensive rubella elimination strategy.	
	Balance between benefits and harms	***Favours inter-vention*** ☒	***Favours com-parison*** ☐	***Favours both*** ☐	***Favours neither*** ☐	**Unclear** ☐	Including RCV in the routine programme provides early protection to all infants and decreases the likelihood of them passing the infection on to others. Using a strategy that targets WRA only, creates immunity gaps within the population.	Including RCV in the routine programme has the added benefit of improving measles coverage when a combination vaccine is used.
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention ***No included studies*** ☐	***Very low*** ☐	***Low*** ☐	***Mod-erate*** ☐	***High*** ☒	The confidence in the quality of the evidence related to the strategy used for rubella and CRS elimination is high, within observational studies, a large effect estimated was observed, hence upgraded.	

		Safety of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Mod-erate* ☐ *High* ☒	Where targeted programmes of WRA only have been used, numerous large outbreaks of rubella have been observed with cases of CRS. As a result of these outbreaks, countries have switched their rubella programme to include vaccination into the routine infant program. These programmes have the additional benefit of protecting individuals from rubella infection and its complications.	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐ *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☐ *No important uncertainty or variability* ☒ *No known undesirable outcomes* ☐	The prevention of CRS cases, constitutes an important public health burden that can be easily prevented. Children with CRS are at risk of early death and often have significant morbidities that require additional care, placing burdens on the family, health care system and society at large. Therefore, the selection of a strategy that reduces immunity gaps within a population (i.e. RCV within the routine programme) is an important desirable outcome.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	Since a strategy of CRS control leaves a large proportion of the population unprotected, there are important examples were cases of CRS have occurred. This strategy has not been implemented by any country in the past 14 years.	

RESOURCE USE	Are the resources required small?	*No* ☐	*Un-certain* ☐	*Yes* ☐	*Varies* ☒		Most countries use a combined measles and rubella vaccine. Only 21 countries do not include rubella vaccination in their routine programme.	
	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐		Studies have been conducted on the cost effectiveness of RCV and have shown the vaccine to be cost effective.	
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Re-duced* ☒	*Varies* ☐		Including rubella vaccine in the routine immunization programme as a part of a comprehensive elimination strategy would reduce health inequities by preventing rubella infections and its complications.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention* ☐	*Com paris on* ☒	*Both* ☐	*Neit her* ☐	*Un-clear* ☐	All countries that are using RCV have chosen not to use the strategy of WRA vaccination as a solo strategy. Some countries will use a combination of routine infant programme, catch up campaigns, supplemental immunization activities, and/or vaccination of WRA.	
	Which option is acceptable to target groups?	*Inter-vention*	*Com paris on*	*Both*	*Neit her*	*Un-clear*	A comprehensive strategy for prevention of rubella and CRS would likely be the preferred option since it provides individual protection against rubella and its	

		☐	☐	☒	☐	☐	complications as well as prevention of cases of CRS.			
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☐	*Yes* ☒	*Varies* ☐	Since rubella vaccine can be given in combination with measles vaccine, implementation is feasible. Additionally, routine immunization programmes in the first year of life are better attended than prenatal visits or relying on SIAs that target WRA.		
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 ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation			We recommend the comparison ☐		We recommend against the intervention and the comparison ☐		

	☐ Only in specific contexts or specific (sub)populations
Recommendation (text)	All countries that have not yet introduced rubella vaccine should include RCVs in their immunization programme as a combined MR or MMR vaccine. Gender-neutral delivery of rubella-containing vaccine to infants during high-coverage routine vaccination should be the primary focus, with a catch-up campaign for a wide age range after introduction. In addition, countries might also wish to continue to target women of reproductive age; however, SAGE noted that the strategy for reducing congenital rubella syndrome by vaccinating only women in this age group results in gaps in population immunity that can lead to outbreaks and cases of the syndrome. SAGE therefore recommended discontinuation of this narrow target approach and advised use of a gender-neutral high coverage paediatric vaccination and catch-up strategy.
Implementation considerations	Countries planning to introduce RCVs should have at least 80% coverage of a cohort (MCV) in order to avoid a paradoxical effect. They should also review the epidemiology of rubella; assess the burden of CRS; and establish rubella and CRS prevention as a public health priority.
Monitoring and evaluation	In all stages of rubella control, rubella surveillance should be integrated with the measles surveillance system. This integrated surveillance should recognize the needs specific to rubella because of its impact during pregnancy. Therefore, all febrile rashes in pregnant women should be investigated. Surveillance for CRS complements rubella surveillance, and should be in place in all countries. Rubella surveillance cannot capture every case of rubella since it is frequently mild or asymptomatic. CRS is the most severe outcome of rubella, and the prevention of CRS is the primary reason for rubella vaccination. Thus, the goals for CRS surveillance are linked to national goals for rubella vaccination, including monitoring progress to achieve and maintain elimination. For countries without routine CRS surveillance, active surveillance, including case detection and investigation, should be implemented during and immediately after a rubella outbreak. Other methods for assessing the burden of CRS may include reviewing hospital records, conducting surveys of children who are hearing or visually impaired and determining the cause of their disability, and reporting by clinicians. The need for high quality case based surveillance to document the impact of rubella vaccination will require laboratory-supported surveillance for rubella, CRS surveillance, and molecular epidemiology as outlined in the WHO standards for CRS and rubella surveillance published in 2018.

Research priorities	Research is needed to improve technology and operational aspects of the rubella programme to address barriers to achieving the elimination of rubella and CRS.

[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