

SAGE Evidence to recommendations framework¹

Rubella vaccine PICO question 2:

Detailed evidence 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 2018.¹

Question: Does the evidence support co-administration of measles-rubella (MR)/measles-mumps-rubella (MMR) and yellow fever (YF) vaccines?

Population: Healthy infants aged 9 months – 2 years.

Intervention: Co-administration of MR/MMR and YF vaccines at the same vaccination visit.

Comparison(s): Administration of MR/MMR or YF vaccine individually, or sequentially with a period ≥ 28 days in-between individual vaccinations.

Outcome: Seroconversion and magnitude of antibody response (titers/antibody concentrations) following vaccination with YF and measles, mumps, rubella vaccines.

Background: Yellow-fever endemic countries in the World Health Organization (WHO) African region (AFR) typically administer YF vaccine along with measles or MR vaccine to children at 9 months of age. In endemic countries in the Americas, YF vaccine has traditionally been co-administered at 12 months of age with MMR vaccine, though there are exceptions to this schedule.

The WHO position papers on rubella (2011) and measles (2017) vaccines state that live vaccines should be administered at the same time or at least 4 weeks apart. However, the rubella paper notes a risk for interference if MMR and YF vaccines are simultaneously administered to young children based on the results of a randomized controlled trial (RCT) in Brazil. Since the publication of the 2011 Brazil study, there have been two additional RCTs that evaluated potential interference between MR/MMR and YF vaccine when they are co-administered as compared to sequential or individual administration.

From a programmatic perspective, co-administration of vaccines provides protection at the earliest possible age, maximizes efficient use of healthcare resources, and prevents children from potentially missing the vaccine should they not return for a later vaccination visit. Hence the risk of interference on immunity needs to be weighed against the risk of non-vaccination should administration of one of the vaccines be delayed to a later, scheduled vaccination visit (e.g. 15 or 18-month visits).

¹ Working Group report, available at <http://www.who.int/immunization/sage/meetings/2018/october/en/>, accessed February 2019.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION.
PROBLEM	Is the problem a public health priority?	No <input type="checkbox"/>	Un-certain <input type="checkbox"/>	Yes <input checked="" type="checkbox"/>	Varies by setting <input type="checkbox"/>	In 2016 there were 22,361 rubella cases reported to the WHO but this is considered a substantial underestimate of the true number of cases as the combined measles-rubella surveillance conducted by most countries is insensitive for rubella. As rubella vaccine is always combined with measles vaccine, the burden of measles is also a significant factor in vaccination policy. In 2017 it was estimated that there were >6.7 million measles cases and >109,000 measles-related deaths. For YF, a 2013 modeling study estimated that there were 84 000–170 000 severe cases with 29 000–60 000 deaths that year in Africa. Both of these diseases can be prevented through vaccination.	The WHO recommends that two doses of MR/MMR are administered to children in every country worldwide and that YF vaccine is administered to all children in YF-endemic areas, including 34 countries in Africa and 13 in South America that are endemic or have areas that are endemic for YF.
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	No <input type="checkbox"/>	Un-certain <input type="checkbox"/>	Yes <input checked="" type="checkbox"/>	Varies <input type="checkbox"/>	The desirable anticipated effects are higher vaccination coverage with both vaccines as co-administration enables vaccination with both vaccines during the first year of life. Vaccination coverage data from 4 countries in the Pan American Health Organization (PAHO) region show higher coverage when MMR and YF are co-administered at 12 months as opposed to a schedule with MMR at 12 months and YF at 15 or 18 months. Coverage data from the AFRO region shows that measles and YF vaccination coverages at 9 months are substantially higher than measles vaccination coverage at 15 or 18 months.	Co-administration has been shown to provide an opportunity for protection at the earliest possible age, maximize efficient use of resources, and prevent children from potentially missing the vaccine dose should they not return for a later vaccination visit.

<p><u>Harms of the intervention</u></p> <p>Are the undesirable anticipated effects small?</p>	<p>No Un-certain Yes Varies</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/></p>	<p>The anticipated undesirable effects are slightly lower antibody titers/concentrations for rubella, mumps, and YF (but not measles vaccine) when the vaccines are co-administered. However, despite being lower in the co-administration group, titers were robust with geometric mean titers being well above the thresholds needed for seroconversion. The clinical implications of the lower titers and whether they will have any effect on long-term immunity are not known.</p>	<p>From a programmatic perspective, there are no harms associated with co-administration. From a caregiver perspective, there could be a perceived harm of having to receive multiple injectable vaccines during a vaccination visit.</p>
<p>Balance between benefits and harms</p>	<p>Favours inter-vention Favours com-parison Favours both Favours neither Unclear</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	<p>Population-level protection from measles, mumps, rubella and YF is a function of both the immune response to the vaccine and vaccination coverage. Coverage data suggest that co-administration will result in the highest coverage, while studies show that co-administration results in lower antibodies titers/concentrations for rubella, mumps and YF (but the clinical implications of this are unknown).</p>	<p>While co-administration may result in a slightly lower magnitude of antibody response, the programmatic implications of delaying one of these vaccines to a later vaccination visit are likely to be substantial and may have a far greater impact on population immunity. However, sequential administration is also acceptable as long as vaccination coverage for both vaccines is high.</p>
<p>What is the overall quality of this evidence for the critical outcomes?</p>	<p>Effectiveness of the intervention</p> <p>No included studies Very low Low Moderate High</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>Safety of the intervention</p> <p>No included studies Very low Low Moderate High</p>	<p>Two of the three RCTs had consistent results showing no interference with seroconversion for any antigen. However, one RCT showed decreased seroconversion for rubella, mumps, and YF, but not measles. All studies showed lower antibody titres/concentrations for rubella, mumps, and YF, but not measles.</p>	<p>The data supporting probable higher vaccination coverage with co-administration are consistent across countries; however, a direct comparison (co-administration vs. sequential administration) was possible in only 4 countries of the Americas and an indirect</p>

		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	There were no safety concerns identified in any of the studies.	comparison (MCV1 at 9 months vs. MCV2 at 12/15 months) is available from only a limited number of African countries
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	<i>Important uncertainty or variability</i>	<i>Possibly important uncertainty or variability</i>	<i>Probably no important uncertainty or variability</i>	<i>No important uncertainty or variability</i>	<i>No known undesirable outcomes</i>	<p>The desirable outcome (protection from measles, mumps, rubella, and YF viruses) is very important. This is a function of both immune response and vaccination coverage.</p> <p>The undesirable outcome (lower titers for rubella, mumps and YF) is of relatively less importance since the geometric mean titers were still will above the estimated thresholds needed for potential immunologic protection.</p>	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	<i>No</i>	<i>Probably No</i>	<i>Uncertain</i>	<i>Probably Yes</i>	<i>Yes</i>	<i>Varies</i>	<p>No studies have been conducted to date on the values and preferences of the target population in this specific circumstance.</p> <p>However, studies on the co-administration of multiple injectable vaccines at one vaccination visit have shown that although caregivers often express preference for fewer injections at a vaccination visit, they are generally accepting of multiple injections at one visit.</p> <p>Caregiver preferences are indirectly reflected by vaccination coverage data indicating higher coverage for vaccines administered earlier in life.</p>
RES		<i>No</i>	<i>Un-certain</i>	<i>Yes</i>	<i>Varies</i>			The resources required for co-administration of vaccines are likely

	Are the resources required small?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		fewer than administration at separate visits because there are fewer visits required for both the child and the health center.	
	Cost-effectiveness	<i>No</i>	<i>Un-certain</i>	<i>Yes</i>	<i>Varies</i>	Not assessed; but see prior comments about resources required.		
		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			
EQUITY	What would be the impact on health inequities?	<i>Increased</i>	<i>Un-certain</i>	<i>Reduced</i>	<i>Varies</i>	Data not reviewed; but minimizing the number of visits a family must make to a health facility removes barriers, which typically reduces health inequities.	Co-administration also enables children to be protected at the earliest possible age.	
		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	<i>Intervention</i>	<i>Comparison</i>	<i>Both</i>	<i>Neither</i>	<i>Unclear</i>	Co-administration is currently the standard of care in most YF-endemic countries.	This has not been formally assessed. While co-administration is used in the majority of YF-endemic countries in AFRO, sequential administration is used in several PAHO countries. Co-administration likely has higher acceptance because it optimizes resources, enables protection at the youngest possible age, and maximizes coverage
		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	Which option is acceptable to target group?	<i>Intervention</i>	<i>Comparison</i>	<i>Both</i>	<i>Neither</i>	<i>Unclear</i>	This has not been formally assessed. Co-administration is currently the standard of care in most YF-endemic countries.	While co-administration is used in the majority of YF-endemic countries in AFRO, sequential administration is used in several
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		

		<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		PAHO countries. Co-administration is likely to have higher acceptance because minimizes the number of clinic visits needed and enables protection at the youngest age possible.					
FEASIBILITY	Is the intervention feasible to implement?	<i>No</i> <input type="checkbox"/>	<i>Probably No</i> <input type="checkbox"/>	<i>Uncertain</i> <input type="checkbox"/>	<i>Probably Yes</i> <input type="checkbox"/>	<i>Yes</i> <input checked="" type="checkbox"/>	<i>Varies</i> <input type="checkbox"/>	Co-administration is already the standard of care in most YF-endemic countries.	
	Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings <input type="checkbox"/>	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings <input type="checkbox"/>	The balance between desirable and undesirable consequences <i>is closely balanced or uncertain</i> <input type="checkbox"/>	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings <input checked="" type="checkbox"/>	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings <input type="checkbox"/>			
	Type of recommendation	We recommend the intervention ⁱⁱ <input checked="" type="checkbox"/>	We suggest considering recommendation of the intervention <input type="checkbox"/> Only in the context of rigorous research <input type="checkbox"/> Only with targeted monitoring and evaluation		We recommend the comparison ⁱⁱ <input checked="" type="checkbox"/>	We recommend against the intervention and the comparison <input type="checkbox"/>			

	<input type="checkbox"/> Only in specific contexts or specific (sub)populations
Recommendation (text)	SAGE therefore recommended that WHO maintain its current guidance that MR/MMR and YF vaccines be administered at the same visit or at least 4 weeks apart (the schedule that maximizes coverage of all antigens in national vaccination schedules) and that WHO remove all cautionary statements about co-administration.
Implementation considerations	For most countries, this is confirmation that their current schedule is acceptable and they do not need to implement a new strategy. The five YF-endemic countries that have not yet introduced YF vaccine should consider a schedule that will maximize coverage with both vaccines. The four countries in the PAHO region that currently provide MMR & YF sequentially should review their vaccine coverage data to determine whether this is the optimal schedule for their country.
Monitoring and evaluation	Monitoring of vaccination coverage should be continued, to ensure that maximum coverage is achieved, regardless of the vaccination schedule selected.
Research priorities	SAGE stated that additional research should be conducted to determine whether the lower titers or antibody concentrations against rubella, mumps and YF observed after co-administration affect long-term immunity and cause secondary vaccine failures.

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>

ii SAGE recommended that WHO maintain its current guidance that MR/MMR and YF vaccines be administered at the same visit or at least 4 weeks apart (the schedule that maximizes coverage of all antigens in national vaccination schedules)