SAGE evidence to recommendations framework[i]

More evidence on the WHO policy for recommending routine measles vaccine second dose (MCV2) can be found in "Conclusions of the SAGE Working Group on Measles and Rubella August 25-26, Geneva".[1]

Question: Should SAGE recommend the removal of the criterion that MCV2 only be given if MCV1 coverage is >80% for the introduction of routine measles second dose as stated in the 2009 measles vaccine position paper.[2]

Population: Children.
Intervention: Routine administration of a 2nd dose of measles (-containing) vaccine (MCV2).
Comparison(s): Introduction of MCV2 only in case of fulfilling the criterion for introduction as outlined in the 2009 WHO position paper on measles vaccine.[2]
Outcome: Cases of measles.

Background: In light of the following considerations and in the interest of advancing progress towards measles control and elimination, SAGE was requested to consider whether it is appropriate at this time to remove the introduction criterion for MCV2 published in the 2009 WHO Measles Vaccine position paper. WHO's current policy recommendation, as provided in the 2009 Measles Vaccine Position Paper, is that all children should receive two doses of measles-containing vaccine: "Reaching all children with 2 doses of measles vaccine should be the standard for all national immunization programmes."

The 2009 position paper provides the following criterion for introduction of routine MCV2:
"MCV2 may be added to the routine immunization schedule in countries that have achieved >80% coverage of MCV1 at the national level for 3 consecutive years as determined by the most accurate means available. In general, countries that do not meet this criterion should prioritize improving MCV1 coverage and conducting high-quality follow-up supplemental immunization activities (SIAs), rather than adding MCV2 to their routine schedule."

Rational for the introduction of the criterion was that routine introduction of MCV2 would distract from efforts to improve MCV1, as well as the observation that countries with weaker systems did not reach high MCV2 coverage.

As of December 2015, the vast majority of countries in the world are implementing a 2-dose routine measles vaccination schedule (160/194, or 82% of countries) and global coverage of MCV2 is estimated at 61%. Of the 33 countries yet to introduce MCV2 into their national immunization schedule, 10 already meet the WHO MCV2 introduction criteria (Bolivia, Comoros, Congo, Dominican Republic, Honduras, Lao People's Democratic Republic, Namibia, Nicaragua, Solomon Islands and Uganda). For the remaining 23 countries, 6 have high or improving coverage, and are close to meeting the introduction criterion; 7 have MCV1 coverage close to 70% or above; and 10 have low coverage. The accumulated evidence demonstrates that both groups of countries (those meeting and those not meeting the introduction criterion) show a trend of increased routine MCV2 coverage during the first five years after introduction.

With the accumulation of 6 years of implementation experience, there are a number of considerations that have emerged which call into question the continued usefulness of the MCV2 introduction criterion.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION

[1] http://www.who.int/immunization/sage/meetings/2016/october/2_MCV2deliberations_YellowBookFinal.pdf?ua=1, accessed Jan 2017
[2] WHO 2009. Measles Vaccines: WHO Position Paper. WER No. 35, 2009. 84. Pp. 349-360.

PROBLEM	Is the problem a public health priority?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	Particularly in settings in which measles virus continues to circulate (which describes most countries without routine MCV2), children who either do not receive a first dose or who fail to seroconvert are at risk of contracting measles.	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	Administration of two doses of measles containing vaccine is more effective than one dose in protecting children against measles. Routine provision of MCV2 closes potential immunity gaps in previously unvaccinated children or in children who have failed to seroconvert after the first dose. Having routine MCV2 in the 2nd year of life signals to health workers that measles vaccination is indicated and catching up MCV1 beyond 12 months of age is in fact good practice, suggesting that health care workers should not reject children over 12 months of age. An MCV2 contact at 15 – 18 months can further help build a 2nd year of life platform, which can be used for delivering other vaccines (e.g. Men A; PCV if using a 2+1 alternative schedule, DTP4 booster doses). An MCV2 contact can also be used for catching up any missed vaccination doses and therefore help towards improving completion of the immunization schedule and fully immunized child coverage. In addition, the proposed intervention may improve the recording and monitoring of administered doses- Recommending a two-dose routine schedule for all countries (without any criteria) would globally standardize the recording of at least two doses. Further, if may reduces MCV wastage rate by 40%. Experience comparing 1 dose YF vs 2 dose MCV shows the following	

			difference. Niger: 15.2% vs 9.0% (40% difference) Senegal: 27.1% vs 10.2% (62% difference)	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	The data indicate that routine MCV2 likely does not adversely impact MCV1 coverage; routine MCV2 may in fact increase the number of children who receive MCV1 (see Figure 3 of Working Group report[1]). Further, measles (-containing) vaccines are safe to use. Whereas an increased risk of febrile seizures has been documented following the first dose of combined MMRV vaccine[3] vs MMR+V, this effect was not seen after administration of a second dose of MMRV vs. MMR+V.[4]	
	Balance between benefits and harms	*Favours intervention* ☒ *Favours comparison* ☐ *Favours both* ☐ *Favours neither* ☐ *Unclear* ☐	Balancing benefits and harms, the intervention is favoured.	

[3] GRADE Table. Risk of febrile seizures after first dose of MMRV in immunocompetent children (9months to 12 years) http://www.who.int/immunization/position_papers/mmrv_grad_safety.pdf?ua=1, accessed Jan 2017.
[4] WHO 2014. Varicella and herpes zoster vaccines: WHO position paper, June 2014. WER No. 25, 2014. 89. Pp. 265-288.

	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention No included studies ☐ Very low ☐ Low ☐ Moderate ☐ High ☒ Safety of the intervention No included studies ☐ Very low ☐ Low ☐ Moderate ☒ High ☐	Two doses of measles containing vaccine are more effective than one dose in protecting against measles (High level of scientific evidence).[5] Evidence supports a moderate degree of confidence in the estimate of the effect that incidence of serious adverse events following measles vaccination is low.[6]	

[5] GRADE table on the effectiveness of two doses of measles vaccine versus one dose in young children and adolescents http://www.who.int/immunization/documents/measles_grad_effectiveness.pdf?ua=1, accessed Jan 2017

[6] GRADE table on Safety of the measles vaccine in young children and adolescents: http://www.who.int/immunization/documents/measles_grad_safety.pdf?ua=1, accessed Jan 2017

VALUES & PREFERENCES	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects? *Important uncertainty or variability* ☐ *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☐ *No important uncertainty or variability* ☒ *No known undesirable outcomes* ☐	No evidence available, though it is assumed that there is no important uncertainty or variability in respect to the desirable and undesirable outcomes.		

RESOURCE USE	Are the resources required small?	*No* ☐ *Uncertain* ☐ *Yes* ☐ *Varies* ☒	Additional resources may be needed to introduce MVC2 into routine immunization. Creating an additional platform for vaccination during the second year of life may be an opportunity to administer several antigens within one health care visit and therefore even reduce overall costs to the health care system.	
	Cost-effectiveness	*No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐	No evidence available, though it is assumed that administering MCV2 through routine immunization more cost-effective than administering MCV2 via immunization campaigns. Further, routine MCV2 administration may reduce wastage rate.	

EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☒ Varies ☐	In countries that do not meet the MCV2 introduction criteria, children born between campaigns do not have equitable access to two doses of measles vaccine. The current recommendation is that reaching all children with 2 doses of measles vaccine should be the standard for all national immunization programmes. However, depending on the timing of their birth, some children have to wait up to three years for the next follow up campaign in order to receive a second dose of measles vaccine. Particularly in settings in which measles virus continues to circulate (which describes most countries without routine MCV2), children who either do not receive a first dose or who fail to seroconvert are at risk of contracting measles. The absence of routine MCV2 likely increases the interval before they receive a dose through supplementary services and thus decreases their access to measles vaccine and increases their risk of morbidity and mortality associated with measles. Parents/guardians have the right to access a primary vaccination schedule that provides full individual protection for their children, regardless of when they are born.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	In light of the balance of benefits vs harms, it is assumed that the intervention is acceptable to most key stakeholders.	

	Which option is acceptable to target group?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Better MVC2 coverage and reducing the number of health care visits by administering several antigens during a second year of life platform may be favourable to the target population. Adding a routine measles dose during the second year of life may in fact also increase MCV1 coverage as more children access vaccination services and barriers to administering a dose of measles vaccine after 12 months of age are overcome.		
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	Measles vaccine after 12 months of age will integrate in the already promoted second year of life platform. In some countries this platform still needs development.		

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 ☐ Only in specific contexts or specific (sub)populations	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	SAGE was requested to consider the removal of the criterion for the introduction of routine measles second dose as stated in the 2009 measles vaccine position paper.[2] SAGE recommended that a routine second dose of MCV should be added to national immunization schedules in all countries regardless of level of MCV1 coverage. The removal of the introduction criterion would help improve equity of access to vaccine in countries with weaker immunization systems as well as allowing these countries time to improve their coverage with the second routine dose. And adding a routine MCV2 can serve to establish a well-child visit in the second year of life, provide a timely opportunity for catch-up in children who missed MCV1 or any other vaccine, potentially reduce MCV wastage, and, based on current evidence, does not negatively impact MCV1 coverage. SAGE emphasized that children older than 24 months should also be checked for missed vaccinations and be vaccinated as needed.			
Implementation considerations	Some countries may require programme guidance to establish or utilize existing platforms to offer MCV2 along with a package of vaccination and other health services.			
Monitoring and evaluation	SAGE stressed that the accumulation of susceptible persons at both the national and subnational level should continue to be monitored to identify and address immunity gaps.			
Research priorities				

[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/