SAGE evidence to recommendations framework[i]

More) can be found in the Report to SAGE on Evidence Supporting Measles Revaccination for HIV-infected Children Receiving Highly Active Antiretroviral Therapy[1]

Question: Should HIV-infected children receiving highly active antiretroviral therapy be revaccinated against measles?

Population: HIV-infected children receiving highly active antiretroviral therapy
Intervention: Revaccination with measles-containing vaccine
Comparison: No revaccination with measles-containing vaccine
Outcome: Immunogenicity conferred by measles vaccine

Background: Human immunodeficiency virus (HIV)-infected children are at increased risk of measles morbidity and mortality and could play a role in sustaining measles virus transmission in regions of high HIV prevalence. Protective antibody concentrations wane following measles vaccination of HIV-infected children as a consequence of impaired immunity. Until the widespread introduction of antiretroviral therapy, due to the high mortality rate of HIV infected children a sizeable pool of measles susceptible children was not build-up. Highly active antiretroviral therapy (HAART) is effective in prolonging survival in HIV-infected children by suppressing viral replication and restoring immune function. However, immune reconstitution in children is primarily achieved through the generation of naïve T and B lymphoctyes rather than the expansion of memory lymphocytes and antiretroviral therapy does not restore measles vaccine-induced immunity established prior to therapy. As a consequence, HIV-infected children are at increased risk of measles morbidity and mortality despite measles vaccination. In countries with a high prevalence of HIV infection, susceptible children receiving HAART could become sufficiently numerous to sustain measles virus transmission despite high levels of measles vaccine coverage. The 2009 World Health Organization (WHO) position paper on measles vaccines recommended measles vaccination of HIV-infected children who are not severely immunosuppressed and measles vaccine may be administered as early as six months of age in regions of high measles incidence without recommendations on revaccination after immune reconstitution with antiretroviral therapy.[2]

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	An increasingly large number of HIV-infected children will receive antiretroviral therapy and these children are at increased risk of measles because of poor antibody responses following vaccination prior to initiation of HAART. These children are at risk of increased measles mortality and morbidity and could sustain measles virus transmission despite high levels of measles vaccine coverage. As of December 2013, an estimated 740,000 HIV-infected children in low and middle-income countries were receiving antiretroviral therapy, with 630,300 (85%) residing in Africa (World Health Organization). These	

[1] Report to SAGE: http://www.who.int/immunization/sage/meetings/2015/october/7_Measles_Revaccination_HIV_Infected_Children_Report_SAGE_26_September_2015.pdf?ua=1, accessed Feb 2017

[2] See No. 35, 2009, 84, 349–360

			children represent only 23% (21-25%) of the estimated 3.2 million (2.9 to 3.5 million) children younger than 15 years of age living with HIV.	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	While HAART does not restore measles immunity from previously received vaccine doses, antiretroviral therapy can restore resting memory B cell percentages to normal levels, necessary for long-term antibody responses following revaccination. Several studies have been conducted on the response to measles vaccination or revaccination after initiating HAART and suggest that children receiving HAART are more likely to respond to revaccination than children not receiving HAART.	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	The evidence does not demonstrate a serious risk in using measles vaccine in HIV-positive children. Although millions of doses of measles vaccine have been administered to HIV-positive children, only 1 case report was identified that suggested possible severe adverse events following immunization. [3]	
	Balance between benefits and harms	*Favours intervention* ☒ *Favours comparison* ☐ *Favours both* ☐ *Favours neither* ☐ *Unclear* ☐	Balancing benefits and harms, the intervention is favoured.	

[3] See No. 35, 2009, 84, 325-32

	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 ☐	We are moderately confident that measles revaccination of HIV-infected children receiving highly active antiretroviral therapy improves measles vaccine immunogenicity and efficacy.[4] Measles immunization is not associated with an increased risk of serious adverse events, though the absence of randomized controlled trials the quality is of very low level of scientific evidence.[5]	
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 re-vaccinate HIV infected children though as HIV-infected children receiving antiretroviral therapy receive intensive follow-up and care, these follow-up visits	

[4] GRADE Table: Measles revaccination of HIV-infected children receiving highly active antiretroviral therapy. http://www.who.int/immunization/policy/position_papers/measles_grad_hiv_revac.pdf, accessed April 2017

[5] GRADE table on Safety of the measles vaccine in HIV-infected children: http://www.who.int/immunization/measles_grad_HIV.pdf?ua=1, accessed Jan 2017

			would facilitate revaccination and would not additional therefore even reduce overall costs to the health care system.	
	Cost-effectiveness	*No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐	No evidence available, though it is assumed that revaccination of HIV infected children would be cost-effective due to the price of the vaccine and the reduction of direct and indirect costs.	
EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☒ *Varies* ☐	In countries with high HIV burden, in particular in low and middle income countries, the reduction of disease burden would positively impact on health inequities.	
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. Further, revaccination of HIV-infected children should be programmatically feasible due to existing contacts with the health system.	
	Which option is acceptable to target group?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Decreasing burden of measles-related morbidity and mortality in HIV infected children by revaccination is presumed to be acceptable to the target population. HIV-infected children receiving antiretroviral therapy receive intensive follow-up and care, these follow-up visits would facilitate revaccination and no additional visit to the health care facility would be needed.	

FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐		Due to the intensive follow-up in HIV-infected children receiving antiretroviral therapy, the option would likely be feasible to implement.		
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 recommended that an additional dose of MCV be administered to HIV-infected children receiving HAART following immune reconstitution. If CD4+ T lymphocyte counts are being monitored, an additional dose of MCV should be administered when immune reconstitution has been achieved, e.g. when the CD4+ T lymphocyte count reaches 20%–25%. Where CD4+ T lymphocyte monitoring is not available, children should receive an additional dose of MCV 6–12 months after initiation of HAART. Current evidence is insufficient to recommend an additional dose for children who start HAART prior to the first dose of MCV.[6]					

[6] See No. 50, 2015, 90, 681–700

Implementation considerations	The care of HIV-infected children is typically delivered at specialized clinics and not at maternal and child health clinics where routine vaccines are administered. Thus, this policy to revaccinate HIV-infected children against measles will require coordination between the clinics that provide HIV care and those that provide routine immunizations to children.
Monitoring and evaluation	
Research priorities	SAGE requested evidence on the need for measles revaccination of HIV-infected adolescents and adults. Further research is needed to monitor the long-term immune responses to measles vaccine in HIV-infected children revaccinated after starting HAART and in HIV-infected children starting HAART prior to receiving their first dose of MCV.

[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/, accessed February 2017