Should an additional dose of measles-containing vaccine be recommended for HIV-infected adolescents and adults?

Introduction

At the October 2015 meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization, SAGE recommended that an additional dose of measles-containing vaccine be administered to HIV-infected children receiving highly active antiretroviral therapy (HAART) following immune reconstitution. In considering this recommendation, SAGE requested evidence on the need for revaccination of HIV-infected adolescents and adults. This report summarizes the available evidence and provides the basis for policy recommendations.

For the purposes of this review, HIV-infected adolescents and adults refer to individuals not infected through mother-to-child HIV transmission. Although an increasing number of perinatally-infected children are surviving into adolescence and adulthood, HIV infection commonly precedes exposure to measles vaccine or wild-type virus in these individuals. Consequently, immune responses to measles vaccine develop in the context of a compromised immune system. This temporal sequence is inverted in HIV-infected adolescents and adults who acquire HIV infection later in life through sexual or other modes of HIV transmission after exposure to measles vaccine virus. This latter group of HIV-infected adolescents and adults is the focus of this review.

Current recommendations on measles vaccination of HIV-infected adolescents and adults

Current recommendations on measles vaccination of HIV-infected adolescents and adults support vaccination of those who are potentially susceptible and not severely immunosuppressed. The World Health Organization's position paper on measles vaccines published in April 2017 states:

> "Given the severe course of measles in patients with AIDS, measles vaccination should be routinely administered to potentially susceptible, asymptomatic HIV-infected children and adults. Vaccination may even be considered for those with symptomatic HIV infection if they are not severely immunosuppressed according to conventional definitions."

The Advisory Committee on Immunization Practices in the United States recommends two doses of MMR in HIV-infected adults without immunologic evidence of severe immunosuppression and measles immunity.

> "Adults with human immunodeficiency virus (HIV) infection and CD4+ T-lymphocyte count ≥200 cells/μl for at least 6 months who do not have evidence of measles, mumps, or rubella immunity should receive 2 doses of MMR at least 28 days apart. Adults with HIV infection and CD4+ T-lymphocyte count <200 cells/μl should not receive MMR."

No current guidelines recommend measles revaccination of HIV-infected adolescents or adults after immune reconstitution with HAART.

Burden of measles in HIV-infected adolescents and adults

Outside of case reports and small case series, limited data exist on the burden of measles in HIV-infected adults, although large measles outbreaks have occurred in populations with a high prevalence of HIV infection, including South Africa (2009-2011) and Malawi (2010). Eight cases of measles inclusion body encephalitis were reported in immunocompromised, HIV-infected adults in South Africa. No published data are available on the incidence of measles or disease severity in HIV infected versus non-infected adults in the same population to determine if HIV-infected persons are at higher risk of disease or death.

Systematic review of measles seroprevalence and measles vaccine immunogenicity and safety in HIV-infected adolescents and adults

To provide SAGE with evidence on the need for revaccination of HIV-infected adolescents and adults, we conducted a systematic review of measles seroprevalence and measles vaccine immunogenicity and safety in HIV-infected adolescents and adults. This systematic review consisted of a search of Medline (Ovid), Embase, Cohrane Library, PubMed, LILACS, INDMED, and WHO GHL databases to identify studies published from the date of establishment of each database to March 16, 2017. The search terms were adapted for each database and included HIV-related keywords in conjunction with measles vaccine-related keywords. References of included studies and relevant reviews were further reviewed to capture pertinent publications not identified in the database search. Search results from each database were merged and duplicates removed. The records were imported into Covidence online software (Veritas Health Innovation) to facilitate screening and full-text review. Titles and abstracts were reviewed by two independent reviewers to exclude irrelevant studies. The remaining studies underwent full-text review by two independent reviewers using pre-specified inclusion and exclusion criteria. Disagreements between reviewers were adjudicated to achieve consensus. Exclusion criteria included review articles, studies in non-human species or studies published in non-English languages. We further excluded studies limited to children younger than 18 years of age or those who were perinatally-infected. Relevant data were extracted independently by two reviewers using standardized data extraction forms and imported into Stata statistical software version 14 (StataCorp). Due to significant heterogeneity in study methodology and outcome reporting, meta-analysis was not considered appropriate. This heterogeneity included differences in the time between exposure to measles virus (wild-type or vaccine) and immunological testing, assay methodology, thresholds to determine seropositivity, and the proportion of participants receiving antiretroviral therapy (ART). The database search identified 1,133 unique publications of which 30, published between 1991 and 2017, were judged to meet inclusion criteria (Figure 1).

Measles seroprevalence in HIV-infected adolescents and adults

Twenty-seven studies involving 9,607 HIV-infected adolescents and adults reported estimates of the proportion who were measles seropositive (Figure 2). History of measles or measles vaccination was generally poorly documented. The median measles seroprevalence was 92% (IQR: 85.2 %-95.0%). Ten studies included an HIV-uninfected comparison group but no study reported statistically significant differences in measles seroprevalence between HIV-infected and HIV-uninfected participants (Figure 3). Three of seven studies that quantified measles antibody levels reported significantly lower antibody levels in HIV-infected participants compared to HIV-uninfected controls, although the clinical and public health impact of these differences is unclear. Eleven studies reported younger age or more recent birth cohort as a

significant risk factor for measles seronegativity, consistent with the hypothesis that measles seroprevalence is higher among HIV-infected populations with a higher risk of exposure to wild-type measles virus.

Immunogenicity of measles-containing vaccines in HIV-infected adolescents and adults

Six studies involving 109 seronegative HIV-infected adults evaluated the immunogenicity of measles-containing vaccine. There was significant heterogeneity across these studies: the dates of publication ranged from 1993 to 2016 and follow-up ranged from 3 weeks to 24 months post-vaccination**.** Measles vaccine immunogenicity, defined by seropositivity at end of follow up, ranged from 0% to 56% (median 39%). Immunogenicity appeared to be higher in more recent studies conducted after the widespread introduction of ART, but the published data did not allow for more direct assessment of the impact of ART on measles vaccine immunogenicity in HIV-infected adolescents and adults. Of the three immunogenicity studies with an HIV-uninfected comparison group, only one study detected a statistically significant lower seroprevalence among HIV-infected adults (p=0.002; Belaunzaran-Zamudio et al., 2009).

Three of six studies on MCV immunogenicity included interim time points after vaccination that demonstrate waning of vaccine-derived immunity among HIV-infected adults. One study reported similar antibody responses 3 months after vaccination between HIV-infected and uninfected participants (81% vs 86% seropositive) but significantly lower rates of seropositivity by 12 months among HIV-infected adults (35% vs 81%). However, similar cellular immune responses as measured by antigen-specific T-cell proliferation were observed at all time points (Belaunzaran-Zamudio et al., 2009).

Safety of MCVs in HIV-infected adolescents and adults

Four studies assessed the safety of measles-containing vaccines in HIV-infected adolescents and adults and no severe adverse events were reported. Our search identified one well-publicized case report of fatal pneumonitis possibly attributable to measles vaccine virus. A 21-year-old man with AIDS and undetectable CD4+ T-lymphocyte count presented 11 months after receiving a second dose of measles vaccine. He was found to have characteristic multinucleated giant cells with intranuclear and intracytoplasmic inclusions on lung biopsy and measles vaccine virus was identified in lung tissue.

Evidence to inform SAGE recommendations

1. The quality of evidence is low that measles seroprevalence does not differ between HIV-infected and uninfected adolescents and adults as it is based on cross-sectional observational studies.
2. The quality of evidence is very low on the immunogenicity of measles vaccine in HIV-infected adolescents and adults.
3. There is confidence in the conclusion that an additional dose of measles-containing vaccine is not warranted for HIV-infected adolescents and adults receiving antiretroviral therapy.

Draft Recommendations

Current World Health Organization recommendations are that measles vaccination should be routinely administered to potentially susceptible, asymptomatic HIV positive children and

adults. Vaccination may be considered for those with symptomatic HIV infection if they are not severely immunosuppressed according to conventional definitions.

1. Studies of measles seroprevalence and measles vaccine immunogenicity among HIV-infected adults do not support the need for an additional dose of measles vaccine following immune reconstitution with HAART.
2. Measles susceptible adults, whether HIV infected or not, may require targeted vaccination efforts to achieve regional measles elimination goals.

Figure 1: Systematic review flow chart

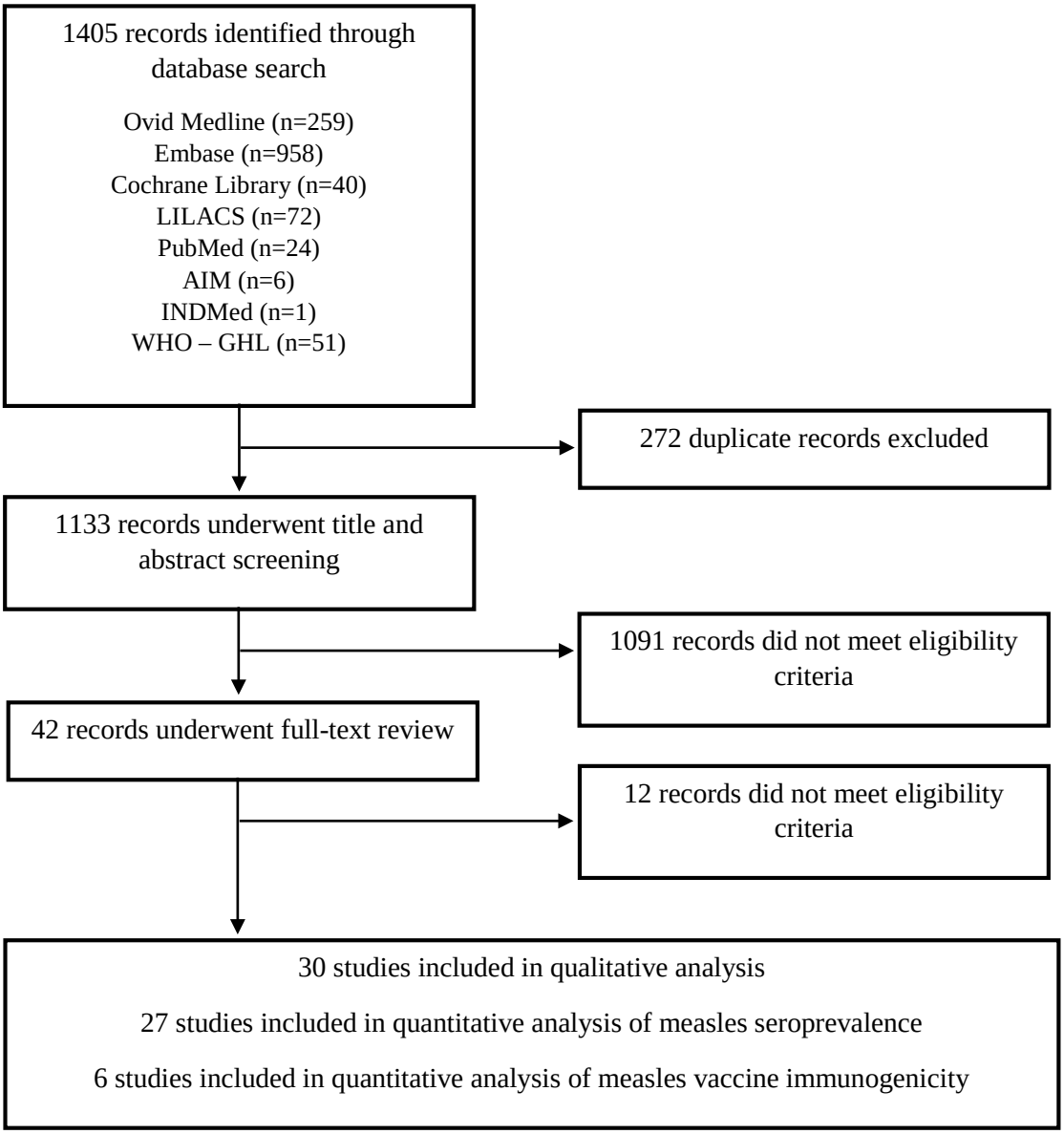

Figure 2: Measles seroprevalence in HIV-infected adolescents and adults

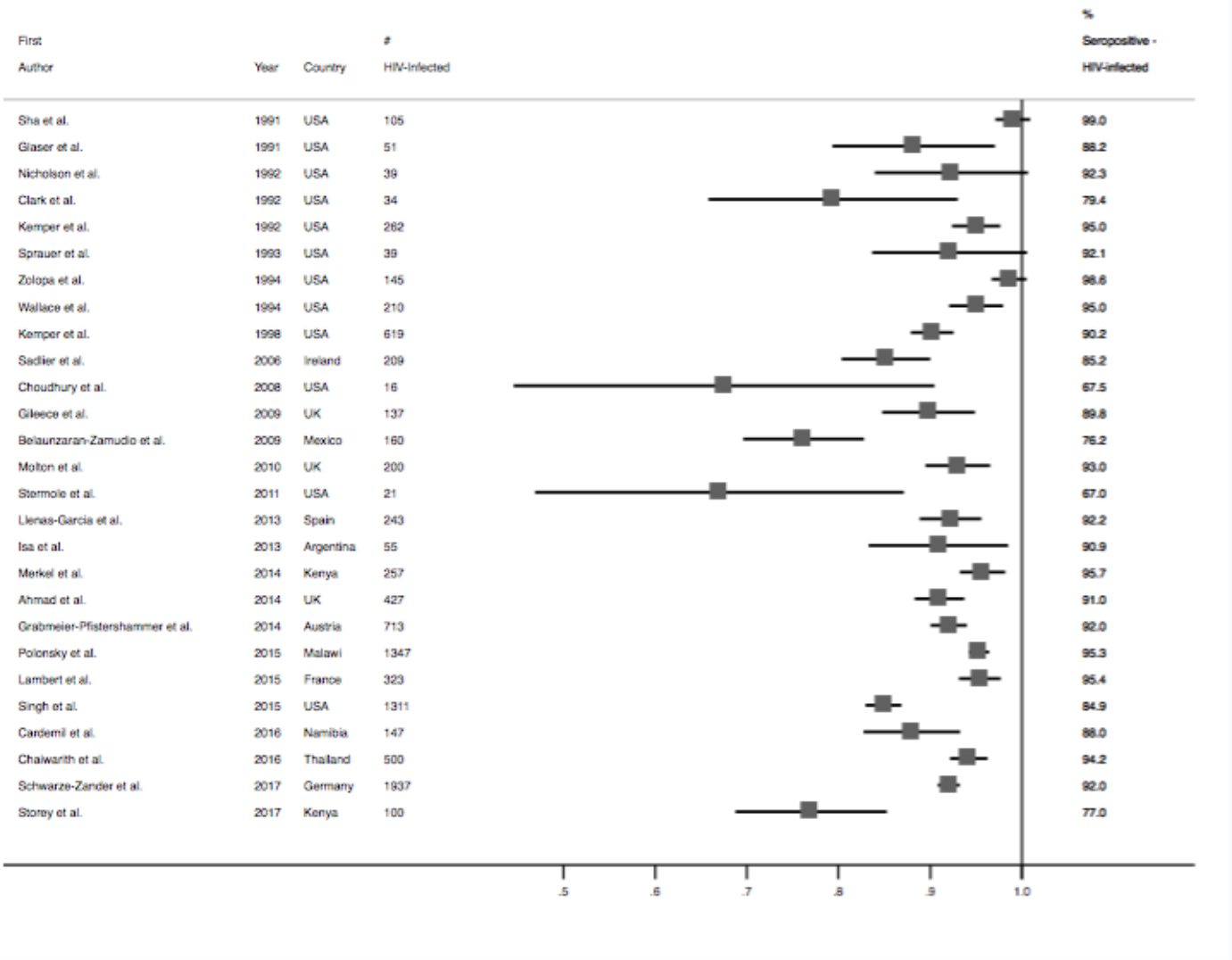

Figure 3: Measles seroprevalence in HIV-infected and uninfected adolecents and adults

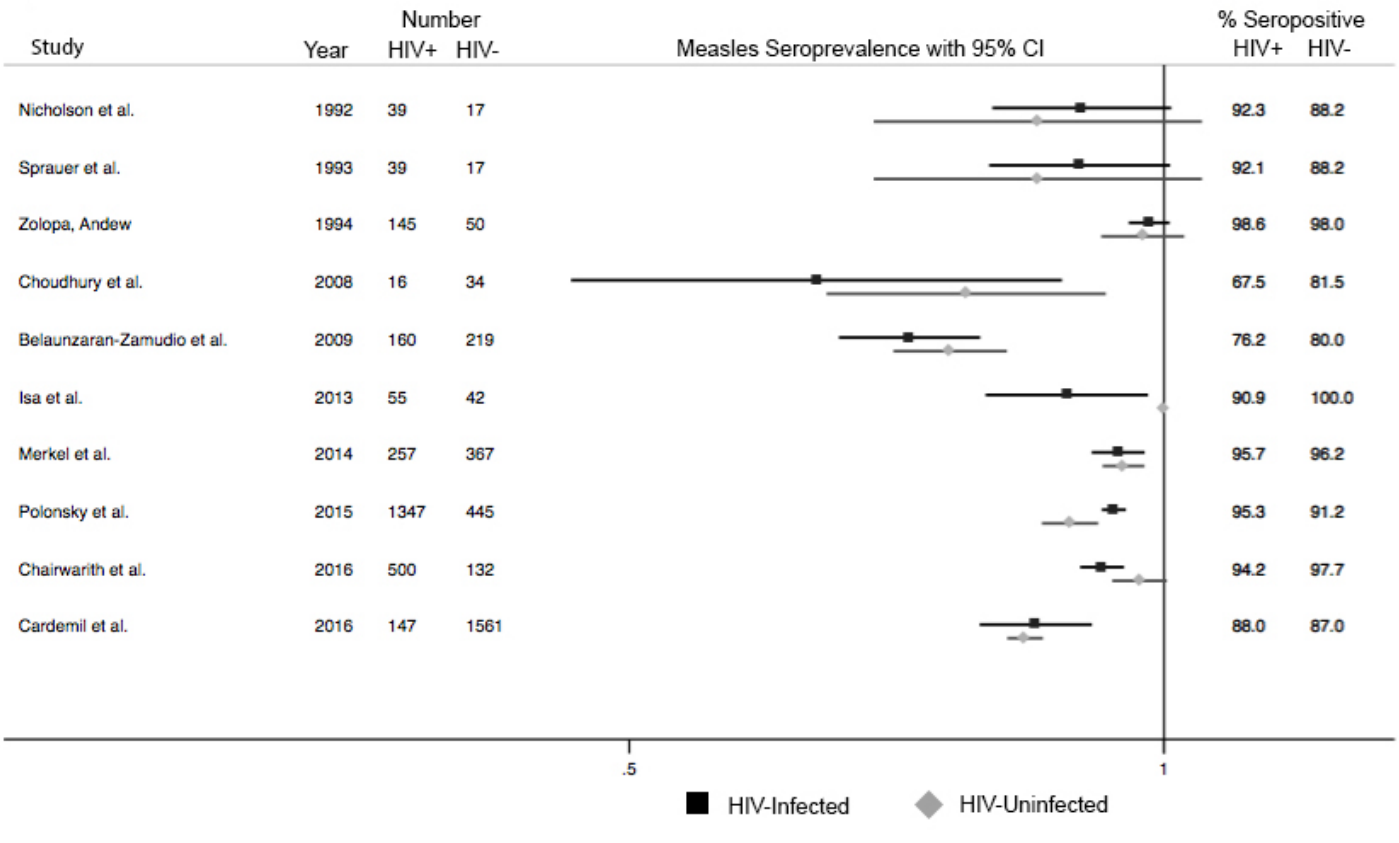

Figure 4: Measles vaccine immunogenicity and safety in HIV-infected adolescents and adults

	Number of HIV-Infected Adults Vaccinated	Number of HIV-Uninfected Adults Vaccinated	% HIV+ receiving ART	End of Follow-Up	Number of HIV+ Seropositive End of Follow-Up	Number of HIV- Seropositive End of Follow-Up	p-value	Interim Time-Points	Severe Adverse Events
Sprauer,1993	3	2	NR	3 weeks	0 of 3 (0%)	1 of 2 (50%)	p>0.05	-	None
Wallace, 1994	6	0	NR	1 year	2 of 6 (33%)	-	-	4 of 6 (67%) HIV+ seropositive at 3 months	None
Belaunzaran-Zamudio, 2009	26	21	84.6%	1 year	9 of 26 (35%)	17 of 21 (81%)	p = 0.002	21 of 26 (81%) HIV+ seropositive at 3 months 19 of 22 (86%) HIV- seropositive at 3 months	None
Stermole, 2011	7	0	NR	Max of 24 months	3 of 7 (43%)	-		-	NR
Singh, 2015	40	0	NR	Mean of 7.2 months	21 of 40 (53%)	-		-	NR
Chaiwarith, 2016	27	2	100%	48 weeks	15 of 27 (56%)	1 of 2 (50%)	p>0.05	20 of 27 (74%) HIV+ seropositive at 8-12 weeks 2 of 2 (100%) HIV- seropositive at 8-12 weeks	None

NR = not reported

Measles Seroprevalence in HIV-infected and HIV-uninfected adolescents and adults

Population: HIV-infected adolescents and adults
Intervention: None
Comparison: HIV-uninfected adolescents and adults
Outcome: Measles seroprevalence

PICO Question: Is the seroprevalence of measles antibodies different among HIV-infected and HIV-uninfected adults?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		10 observational studies	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious[1]	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			Evidence supports a low level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			We have a low level of confidence in the conclusion that that measles seroprevalence is not lower in HIV-infected than uninfected adolescents and adults.

[1] No study showed a statistically difference in measles seroprevalence between HIV-infected and uninfected adults.

References

1. Belaunzarán-Zamudio PF, García-León ML, Wong-Chew RM, et al. Early loss of measles antibodies after MMR vaccine among HIV-infected adults receiving HAART. *Vaccine* 2009; 27:7059-64.
2. Cardemil CV, Jonas A, Beukes A, et al. Measles immunity among pregnant women aged 15-44 years in Namibia, 2008 and 2010. *Int J Infect Dis* 2016; 49:189-95.
3. Chaiwarith R, Praparattanapan J, Nuket K, Kotarathitithum W, Supparatpinyo K. Seroprevalence of antibodies to measles, mumps, and rubella, and serologic responses after vaccination among human immunodeficiency virus (HIV)-1 infected adults in Northern Thailand. *BMC Infect Dis* 2016;16:190.
4. Choudhury SA, Hatcher F, Berthaud V, Ladson G, Hills E, Humphrey A. Immunity to measles in pregnant mothers and in cord blood of their infants: impact of HIV status and mother's place of birth. *J Natl Med Assoc* 2008; 100:1445-9.
5. Isa MB, Pavan JV, Sicilia Don P, et al. Persistence of measles neutralizing antibody related to vaccine and natural infection acquired before HIV infection. *Epidemiol Infect* 2014;142:1708-12.

6. Merkel M, Ben-Youssef L, Newman LP, et al. Seroprevalence of measles IgG among HIV-1-infected and uninfected Kenyan adults. *Int J Infect Dis* 2014;19:103-5.
7. Nicholson JK, Holman RC, Jones BM, McDougal JS, Sprauer MA, Markowitz LE. The effect of measles-rubella vaccination on lymphocyte populations and subpopulations in HIV-infected and healthy individuals. *J Acquir Immune Defic Syndr* 1992;5:528-9.
8. Polonsky JA, Singh B, Masiku C, et al. Exploring HIV infection and susceptibility to measles among older children and adults in Malawi: a facility-based study. *Int J Infect Dis* 2015;31:61-7.
9. Sprauer MA, Markowitz LE, Nicholson JK, et al. Response of human immunodeficiency virus-infected adults to measles-rubella vaccination. *J Acquir Immune Defic Syndr* 1993;6:1013-6.
10. Zolopa AR, Kemper CA, Shiboski S, Hamilton JR, Moss AR, Deresinski SC. Progressive immunodeficiency due to infection with human immunodeficiency virus does not lead to waning immunity to measles in a cohort of homosexual men. *Clin Infect Dis* 1994;18:636-8.

Immunogenicity of MCV in HIV-infected and HIV-uninfected adolescents and adults

Population: HIV-infected adolescents and adults
Intervention: Measles vaccination
Comparison: HIV-uninfected adolescents and adults
Outcome: Measles seroprevalence at end of follow-up

PICO Question: Is the immunogenicity of MCV different among MCV-naïve HIV-infected and HIV-uninfected adolescents and adults?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		3 observational[1]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	Serious inconsitencies[2]	-1
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	Not present	0
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**1**
Summary of Findings	**Statement on quality of evidence**			Evidence supports a very low level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			We have a very low level of confidence in our conclusions regarding the relative immunogenicity of MCV in HIV-infected and uninfected adolescents and adults.

[1] Although these were clinical studies in which measles vaccine was administered to HIV-infected and uninfected adults, there was no randomization, placebo, nor masking of HIV-infection status.
[2] Two of 3 studies found a significant difference in immunological response between HIV-infected and HIV-uninfected vacinees. There is significant heterogeneity in the methodology, point estimates and conclusions.

References

1. Belaunzarán-Zamudio PF, García-León ML, Wong-Chew RM, et al. Early loss of measles antibodies after MMR vaccine among HIV-infected adults receiving HAART. *Vaccine* 2009;27:7059-64.
2. Chaiwarith R, Praparattanapan J, Nuket K, Kotarathitithum W, Supparatpinyo K. Seroprevalence of antibodies to measles, mumps, and rubella, and serologic responses after vaccination among human immunodeficiency virus (HIV)-1 infected adults in Northern Thailand. *BMC Infect Dis* 2016;16:190.
3. Sprauer MA, Markowitz LE, Nicholson JK, et al. Response of human immunodeficiency virus-infected adults to measles-rubella vaccination. *J Acquir Immune Defic Syndr* 1993;6:1013-6.

Safety of MCV in HIV-infected and HIV-uninfected adolescents and adults

Population: HIV-infected adolescents and adults
Intervention: Measles vaccination
Comparison: HIV-uninfected adolescents and adults
Outcome: Occurrence of adverse and serious adverse events

PICO Question: Is the safety of MCV different among MCV-naïve HIV-infected and HIV-uninfected adolescents and adults?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		3 observational[1]	2
	Factors decreasing confidence	Limitation in study design	Serious limitations[2]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	Not present	0
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**1**
Summary of Findings	**Statement on quality of evidence**			Evidence supports a very low level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			We have a very low level of confidence in our conclusion that the safety of MCV is not different in HIV-infected adolescents and adults as compared to HIV-uninfected

[1] Although these were clinical studies in which measles vaccine was administered to HIV-infected and uninfected adults, there was no randomization, placebo, nor masking of HIV-infection status.
[2] Rare, serious adverse events, such as infection with measles vaccine virus, would not have been detected in these studies.

References

1. Belaunzarán-Zamudio PF, García-León ML, Wong-Chew RM, et al. Early loss of measles antibodies after MMR vaccine among HIV-infected adults receiving HAART. *Vaccine* 2009;27:7059-64.
2. Chaiwarith R, Praparattanapan J, Nuket K, Kotarathitithum W, Supparatpinyo K. Seroprevalence of antibodies to measles, mumps, and rubella, and serologic responses after vaccination among human immunodeficiency virus (HIV)-1 infected adults in Northern Thailand. *BMC Infect Dis* 2016;16:190.
3. Sprauer MA, Markowitz LE, Nicholson JK, et al. Response of human immunodeficiency virus-infected adults to measles-rubella vaccination. *J Acquir Immune Defic Syndr* 1993;6:1013-6.