Supplemental measles vaccine antibody response among HIV-infected and -uninfected children in Malawi after 1- and 2-dose primary measles vaccination schedules

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ABSTRACT

Background: The long-term antibody response to measles vaccine (MV) administered at age 6 months with or without subsequent doses is not well documented.

Methods: Measles serum antibody responses were evaluated after a supplemental dose of measles vaccine (sMV) administered at a median age of 20 months among Malawian children who had previously received 2 doses of measles vaccine (MV) at ages 6 and 9 months (HIV-infected and random sample of HIV-uninfected) or 1 dose at age 9 months (random sample of HIV-uninfected). We compared measles antibody seropositivity between groups by enzyme linked immunoassay and seroprotection by plaque reduction neutralization geometric mean concentrations.

Results: Of 1756 children enrolled, 887 (50.5%) received a sMV dose following MV at 9 months of age and had specimens available after sMV receipt, including 401 HIV-uninfected children who received one MV dose at 9 months, 464 HIV-uninfected and 22 HIV-infected children who received two doses of MV at ages 6 and 9 months. Among HIV-uninfected children, protective levels of antibody were found post sMV in 90–99% through ages 24–36 months and were not affected by MV schedule. Geometric mean concentration levels of measles antibody were significantly increased post-sMV among those HIV-uninfected children previously non-responsive to vaccination. Among HIV-infected children, the proportion seroprotected increased initially but by 9 months post-sMV was no higher than pre-sMV.

Conclusions: Our findings support early 2-dose MV to provide measles immunity for young infants without risk of interference with antibody responses to subsequent MV doses administered as part of SIAs.

1. Background

The World Health Organization (WHO) recommends that children be vaccinated with at least two doses of measles vaccine (MV). In areas of the world with high rates of both HIV and measles infection, the World Health Organization recommends that a first MV dose may be offered as early as age 6 months of age, with two additional doses administered through routine services and/or supplemental immunization activities (SIAs) according to the national immunization schedule [1]. Strategies to introduce MV at ages younger than age 9 months must weigh the potential for a lower antibody response due to interference of maternal antibodies and possibly immature immune systems with the risk of developing measles in the first year of life [2,3]. Data on the long-term antibody response to MV administered at age 6 months with or without subsequent doses are inconclusive [4–6]. We have previously demonstrated protective levels of antibody more than a year post-vaccination among HIV-uninfected children in Malawi who were randomized to receive either one MV dose at age 9 months or two MV doses at ages 6 and 9 months [7,8]. However, the two-dose MV schedule did not appear to improve protection among

HIV-infected children beyond that reported by prior studies of vaccination of HIV-infected children at 9 months of age [9]. During the study, a SIA was conducted, which afforded the opportunity to compare antibody responses to the supplemental dose of measles vaccine (sMV) for the two vaccination strategies.

2. Methods

Malawi study of measles vaccination in HIV-infected and -uninfected children

The study design and detailed methods have been described in previous publications [7,8]. Briefly, the study was conducted in Blantyre, Malawi from August 2000 through March 2003, at which time the HIV infection prevalence among women of child bearing age was approximately 33% [10]. During the infant's 14-week routine immunization visit at the Ndirande Health Center, 1327 children born to HIV-uninfected mothers were enrolled and randomized to receive either two doses of standard-titer Edmonston–Zagreb MV (Berna Biotech) at ages 6 and 9 months or one dose at age 9 months; all 429 children born to HIV-infected mothers were assigned to the 2-dose MV group. Adverse events were assessed 7 and 21 days after receipt of any MV dose. Blood was drawn and clinical information was collected at enrollment and during each follow-up appointment scheduled at ages 6, 9, 12, 20, 24, 30, and 36 months. Clinical information was also obtained on outpatient clinic visits, hospitalizations, and deaths. Antiretroviral therapy was not available in the public sector at the time of this study. Previous publications reported the detailed methods, clinical follow-up, loss to follow-up, and the antibody response to early and 9-month MV doses [7,8].

2.1. Evaluation of supplemental measles vaccination

In August of 2002, a nationwide measles vaccination SIA for all children ages 9–59 months was conducted by the Malawi Ministry of Health, in partnership with WHO, and the United Nations Children's Fund. At the time of the SIA, there were no recently reported measles cases near the study region of Malawi, thus approval was received by the Institutional Review Boards and Ministry of Health for parents of children in the measles study aged <20 months to be given the option to defer sMV until age 20–24 months, the planned follow-up age for study children. A revised consent form was developed for the parents/guardians explaining the option to defer vaccination in the SIA. Parents/guardians presenting children for vaccination during the SIA were referred to the study clinic (which was located at a government health center) for sMV receipt when campaign staff recognized the study participation stamp in the immunization card. Therefore children received sMV through the SIA campaign directly, the study clinic during the SIA, or a follow up study clinic visit. Parent/guardian report and immunization cards were used to document sMV receipt at the SIA.

2.2. Measles antibody and HIV detection

Measles serologic testing by enzyme immunoassay (EIA, Trinity Biotech) and HIV-testing by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) were performed at the Centers for Disease Control and Prevention as described previously [7]. To account for documented reductions in EIA sensitivity in serum specimens with lower levels of measles antibody compared with the gold standard plaque reduction neutralization (PRN) [4], specimens from all HIV-infected children and a random selection of HIV-uninfected children with follow-up through the 12 and 24 month study visits were also tested for measles antibody by plaque

reduction neutralization (PRN) at the Food and Drug Administration [8]. Children with specimens randomly selected for PRN testing were representative of the total study population. We defined seropositivity as an immune status ratio >1.1 from the measles EIA assay and a seroprotective antibody titer as a measles PRN antibody titer ≥120 mIU/mL relative to WHO II Reference serum, 66/202 [11].

2.3. Data analysis

In previous publications, children's data were censored at the time of sMV receipt. In the present analysis, we included children who had received sMV >3 months after their routine 9-month MV dose and had data available from at least one specimen collected >28 days following sMV receipt. For each child, we used the specimen taken on the date of sMV or the most recent specimen available prior to sMV to determine the pre-sMV measles antibody levels. We categorized post-sMV specimens according to the number of months since sMV receipt: <3 months, 3 to <6 months, 6 to <9 months, and >9 months. Seven children who seroconverted to HIV after age 12 months were analyzed separately.

Among HIV-uninfected children, we compared responses to sMV among those who had previously received 1- or 2- doses of MV. We also compared responses among HIV-infected and -uninfected children. For each time point, we calculated the proportion seropositive by EIA and seroprotected by PRN and the geometric mean concentration (GMC) of the measles neutralizing antibody levels. The proportion of measles seropositive or seroprotected patients were compared across study groups at each time point using the pairwise *chi*-square comparisons or Fisher's exact tests at time points with a small sample size. The log-transformed neutralizing antibody titers at different time points were compared within and between study groups using a one way analysis of variance and pairwise *t*-tests to identify specific group differences. Stata, version 12 (College Station, TX) was used for analysis.

3. Results

Of 1756 children originally enrolled, 1060 (60.4%) children remained in the study through receipt of the sMV; 887 (83.7%) had antibody data available after sMV receipt. Children in all study groups received sMV at approximately age 20 months, a median of 11 months (interquartile range 9.5–14.6) after receipt of the 9-month routine MV dose (Table 1). The demographic characteristics of children included in this sMV evaluation were similar to the total study population (data not shown) and did not differ among HIV-uninfected study groups (Table 2) [7]. Due to the selection of children for the present study based on the availability of specimen test results following sMV, which occurred during the children's final year of participation, study attrition and mortality rates did not differ according to HIV-infection status; however, as previously reported, HIV-infected children were lost to follow-up in the full study by age 20 months significantly more frequently, with mortality as the leading cause [8]. Consistent with the evaluation of primary vaccination, no serious adverse events were identified following sMV, and rates of outpatient clinic visits, hospitalizations, and deaths were similar 30 days before and 30 days after sMV for each study group (data not shown). A significantly higher proportion of HIV-uninfected children received sMV through the SIA compared with HIV-infected children (29.7% [263/865] vs. 9.1% [2/22]); however, no differences in antibody response was detected according to SIA vs. study clinic sMV.

Children without HIV infection

Prior to sMV, approximately 81% of HIV-uninfected 1- and 2-MV dose recipients were seropositive by EIA, and approximately 89%

Table 1
Percent of children measles antibody positive by EIA or seroprotected by PRN assays before and after a supplemental dose of measles vaccine (sMV) among children randomized to receive routine measles vaccination at 9 months (MV 9) or 6 and 9 months (MV 6&9) of age by HIV infection status. No HIV-exposed children were randomized to receive MV at 9 months only.

MV schedule and HIV infection by measles detection assay type	Measles antibody detected after primary MV (pre-sMV)		Measles antibody detected by number of months following supplementary MV[a]							
			<3 months		3–6 months		6–9 months		>9 months[b]	
	No./No. (%)	p value	No./No. (%)	p value	No./No. (%)	p value	No./No. (%)	p value	No./No. (%)	p value
Enzyme immunoassay										
MV 9 months, HIV-uninfected	327/401 (81.6)	REF	22/22 (100)	–	219/221 (99.1)	REF	139/140 (99.3)	REF	96/101 (95.1)	REF
MV 6&9 months, HIV-uninfected	374/464 (80.6)	NS	41/41 (100)	–	256/268 (95.5)	<0.05	120/129 (93.0)	<0.05	124/132 (93.9)	NS
MV 6&9 months, HIV-infected	8/22 (36.4)	<0.01	3/3 (100)	–	10/15 (66.7)	<0.01	2/5 (40.0)	<0.01	2/8 (25.0)	<0.01
Plaque reduction neutralization										
MV 9 months, HIV-uninfected	183/206 (88.8)	REF	11/11 (100)	–	106/107 (99.1)	REF	92/93 (98.9)	REF	80/81 (98.8)	REF
MV 6&9 months, HIV-uninfected	189/211 (89.6)	NS	22/22 (100)	–	100/103 (97.1)	NS	74/77 (96.1)	NS	89/97 (94.7)	NS
MV 6&9 months, HIV-infected	8/21 (38.1)	<0.01	3/3 (100)	–	11/15 (73.3)	<0.01	2/5 (40.0)	<0.01	2/6 (33.3)	<0.01

[a] The median age at each time of measurement did not differ significantly by study group and was observed as the following: 20.1 months pre-sMV, 24.3 months at <3 months post-sMV, 24.2 months at 3-6 months post-sMV, 27.7 months at 6–9 months post-sMV, and 30.3 at >9 months post-sMV.
[b] The median number of months following sMV included in the >9 months group was 12.1 months with a range of 9.3–24.6 months and interquartile range of 10.3–15.5 months.

Table 2
Demographic characteristics of children randomized to receive routine measles vaccination at 9 months (MV 9) or 6 and 9 months (MV 6&9) of age by HIV infection status.

	MV 9 months, HIV-uninfected (n = 401)	MV 6&9 months, HIV-uninfected (n = 464)	MV 6&9 months, HIV-infected (n = 22)	
	No. (%)	No. (%)	No. (%)	p value
Demographics				
Male	199 (49.6)	221 (47.6)	14 (63.6)	NS
Owns home	139 (34.7)	151 (32.5)	3 (13.6)	NS
>4 kids in the home	84 (21.0)	69 (14.9)	1 (4.6)	0.017
Electricity in home	155 (38.7)	196 (42.2)	9 (40.9)	NS
Running water in home	22 (5.5)	24 (5.2)	4 (18.2)	0.035
Maternal Education > Primary	126 (31.4)	157 (33.8)	4 (18.2)	NS
Paternal Education > Primary	243 (63.0)	291 (65.0)	11 (52.4)	NS
Birthweight <3.0 kg	196 (48.9)	213 (45.9)	8 (36.4)	NS
Nutritional status at sMV[a]				
Stunted	(0.0)	(0.0)	(0.0)	NS
Underweight	87 (21.7)	97 (20.9)	12 (54.5)	0.001
Wasting	97 (20.9)	6 (1.3)	2 (9.1)	NS

[a] The nutritional status z-score cut-off used to define stunting, underweight and wasting from height-for-age, weight-for-age, and height-for-weight was < −2.0.

were seroprotected according to PRN testing (Table 1). Both the sensitivity and specificity of the EIA relative to the PRN assay were 91% (95% CI: 89.9–92.7% and 89.3%– 93.2%, respectively) [8]. The pre-sMV measles neutralizing antibody GMC did not differ significantly according to vaccine schedule (Fig. 1).
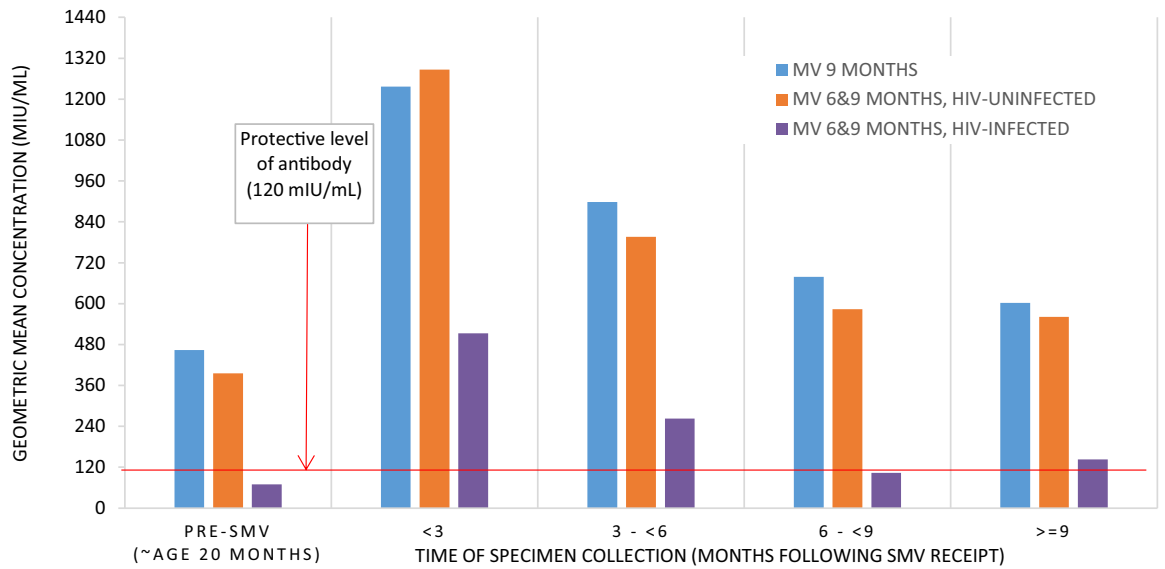
At each time point measured after sMV, the proportion of children seropositive was significantly higher than pre-sMV; most HIV-uninfected children remained both measles seropositive and seroprotected through the end of the study. The measles antibody GMC rose sharply after vaccination, showing a 3-fold increase (Fig. 1), but then fell quickly again such that by >9 months post-sMV the GMCs were only 1.3 and 1.4 times higher than the pre-sMV values among 1- and 2-MV dose recipients, respectively. Further evaluation of GMCs according to children's pre-sMV antibody level demonstrated that pre-sMV seronegative children maintained a 4-fold or higher GMC compared with their pre-sMV values through >9 months post-sMV (pre-sMV GMC range 44–80 mIU/mL vs. >9 months post-sMV GMC range 161–742; p < 0.001, Fig. 2). By contrast, it was the pre-sMV measles antibody positive children whose measles antibody level at >9 months post-sMV had fallen to levels comparable to the pre-sMV values. No significant differences in the measles antibody GMC between 1- and 2-MV dose groups were detected at any time point post-sMV.

Prior to sMV, HIV-uninfected females in both the 1- and 2-dose MV groups had significantly higher measles antibody GMCs than

males (data not shown); similar findings were previously reported [7]. Following sMV, no gender differences were detected at any time point for any study group. In addition, measles antibody response to sMV did not vary according to nutritional status.
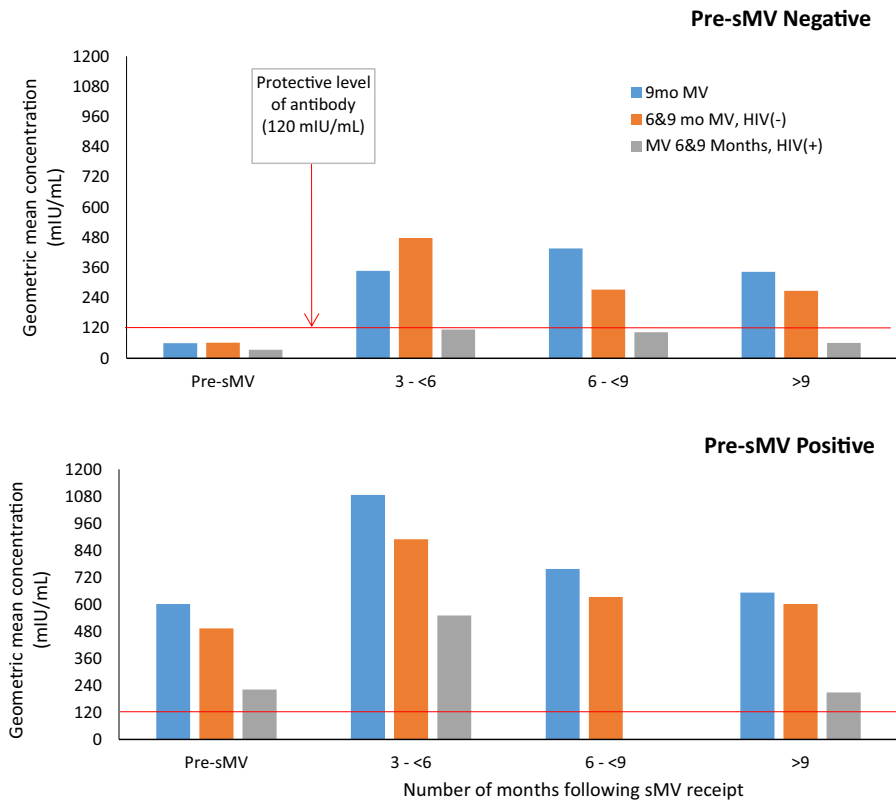
3.1. HIV-infected children

Of 45 HIV-infected children remaining in the study at 12 months of age, 28 (62.2%) met inclusion criteria for the sMV evaluation. Only 38.1% of HIV-infected children were seropositive pre-sMV—significantly lower (p < 0.001) than other study groups (Table 1, Fig. 1). Among 15 HIV-infected children with specimens collected 3–6 months following sMV, a significant increase in the GMC (270 mIU/mL) and the proportion seropositive and seroprotected (66.7% and 73.3%, respectively, p < 0.05) was observed. However, this increase in measles antibody levels was not sustained, as indicated by seropositivity and seroprotection rates at or below 40% at later time points. The pattern of an initial rise in GMCs followed by rapid fall post-sMV was similar to that in the HIV-uninfected groups except that even in those seronegative pre-sMV, a sustained increase in antibody level was not seen (Fig. 2). The proportion of HIV-infected children seropositive and seroprotected did not vary at any time point by nutritional status indicators; however, the pre-sMV antibody titers were significantly lower among

Fig. 1. Geometric mean concentration of measles antibody before and after a supplemental dose of measles vaccine (sMV) among children randomized to receive measles vaccination (MV) at 9 months or 6 and 9 months of age by HIV infection status. No HIV-exposed children were randomized to receive MV at 9 months only. The protective level of measles antibody (120 mIU/mL) is relative to WHO II Reference Serum 66/202.

MEASLES VACCINATION GROUP	GMC (95% CI)	GMC (95% CI)	GMC (95% CI)	GMC (95% CI)	GMC (95% CI)
MV 9 MONTHS	464.1 (395-545)	1236.5 (620-2490)	897.8 (765-1064)	678.6 (572-812)	601.8 (503-721)
MV 6&9 MONTHS, HIV-UNINFECTED	395.4 (347-455)	1286.9 (916-1808)	796.3 (659-953)	584.1 (464-728)	561.2 (469-679)
MV 6&9 MONTHS, HIV-INFECTED	69.4 (37-129)	512.9 (0-6503)	262.4 (130-528)	103.5 (30-354)	142.6 (32-633)

Fig. 2. Geometric mean concentration of measles antibody before and after a supplemental dose of measles vaccine (sMV) according to measles seropositivity pre-sMV, by vaccine schedule and HIV infection status.

underweight children compared with other weight categories (GMC 76 [95%CI: 4–166] vs. 204 [95% CI: 33–327], $p < 0.05$).

Among the 7 children excluded from other analyses due to HIV seroconversion after age 12 months, 5 received sMV after seroconverting to HIV. At the time of sMV, 4 (57.1%) of these children were measles positive by EIA, 5 (71.4%) were seroprotected, and the GMC was 225.0 mIU/mL. Within six months following sMV, 5 of 6 (83.3%) children were seropositive and 5 (83.3%) children were seroprotected; however, it was not the same child testing negative by EIA and PRN. After >9 months following sMV, only 2 of 5 children were seropositive by EIA, although three of four with PRN results available were still considered seroprotected and the GMC was 400 mIU/mL.

4. Discussion

Among HIV-uninfected children, we observed a sustained measles antibody response to sMV among previous MV non-responders that was similar for children who had received either a routine single MV dose at age 9 months or an early, 2-dose MV schedule at ages 6 and 9 months. Consistent with our findings following the 1- and 2-dose MV receipt, we found after sMV that when measured by EIA, measles seropositivity rates were lower among 2-dose than 1-dose recipients, but by the gold standard PRN, rates of seropositivity and seroprotection did not differ significantly by vaccination schedule [8].

We were able to utilize the post-sMV period to systematically evaluate the antibody response to sMV. It is reassuring that receipt of an early MV dose at age 6 months did not adversely affect responses elicited by a routine dose of MV at age 9 months nor the sMV given later among HIV-uninfected children. These findings are consistent with studies that found no evidence of interference to sMV subsequent to an early dose of MV [4,12], and support the approach of recent studies that indicate early MV benefits in reducing infant hospitalization and mortality [13,14]. The sMV clearly increased the proportion of children seroprotected against measles. Among HIV-uninfected children, a sharp rise in the antibody titer was observed in the months immediately following sMV, and was maintained among previous MV non-responders. The observed titer increase among children who were immune prior to sMV was transient and declined by 9 months post-sMV. This corresponds with previous work showing that a boost from additional doses of measles vaccine on measles antibody levels may be relatively short-lived among children who had previously shown an immune response to vaccination [15].

Among HIV-infected children, the sMV led to a transient boost in antibodies which waned rapidly over time, even in those who were not seroprotected pre-sMV. Neither the proportion seroprotected nor the GMC was significantly higher by 9 months post-sMV than pre-sMV. Our findings were consistent with previous studies which demonstrate the rapid decline in vaccine-induced measles antibody titers and a lack of sustained response to MV in HIV-infected children [16]. The very small number of children who developed HIV infection subsequent to primary measles vaccination maintained better measles positivity and seroprotective levels of antibody compared with children who were HIV-infected at the time of primary vaccination. However, the measles antibody levels for these late HIV seroconverters were diminished in comparison with HIV-uninfected children. A review of recent studies indicated that revaccination after immune reconstitution via antiretroviral therapy can result in sustained immune responses to measles [17].

The sMV evaluation had limitations, since the original design did not account for the SIA. As a result, the <3 months post-sMV time period established for early immune response evaluation contained small numbers of children in each group. However, among HIV-uninfected child groups, subsequent time periods were well powered for detection of differences. Due to high mortality and dropout rates among HIV-infected children, our sMV evaluations included only small numbers of HIV-infected children. Finally, our study was conducted prior to routine use of antiretroviral medications and CD4 counts of the children were unavailable, precluding an evaluation of their specific effects on MV antibody responses.

For WHO regions to achieve their goal for measles elimination by 2020, an estimated population immunity of 93–95% must be maintained. Our findings provide support for the WHO measles vaccine delivery strategy that provides an additional opportunity for measles vaccination, and confirm that the sMV is safe and effective for children receiving either early, 2-dose or routine, 1-dose MV. Our findings further suggest that early MV administration can provide measles immunity to a substantial proportion of susceptible young infants without interference of antibody responses to subsequent MV doses administered as part of SIAs.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the CDC. The use of trade names is for identification only and does not imply endorsement by the Department of Health and Human Services or the CDC.

Conflicts of interest

The authors have no conflicts of interest.

References

[1] World Health Organization (WHO). Measles vaccines: WHO position paper. Wkly Epidemiol Rec 2009;84:349–60.

[2] Gans HA, Yasukawa LL, Alderson A, Rinki M, DeHovitz R, Beeler J, et al. Humoral and cell-mediated immune responses to an early 2-dose measles vaccination regimen in the United States. J Infect Dis 2004;190:83–90.

[3] Embree JE, Datta P, Stackiw W, Sekla L, Braddick M, Kreiss JK, et al. Increased risk of early measles in infants of human immunodeficiency virus type 1-seropositive mothers. J Infect Dis 1992;165:262–7.

[4] Carson MM, Spady DW, Beeler JA, Krezolek MP, Audet S, Pabst HF. Follow-up of infants given measles vaccine at 6 months of age: antibody and CMI responses to MMRII at 15 months of age and antibody levels at 27 months of age. Vaccine 2005;23:3247–55.

[5] Garly ML, Bale C, Martins CL, Monteiro M, George E, Kidd M, et al. Measles antibody responses after early two dose trials in Guinea–Bissau with Edmonston-Zagreb and Schwarz standard-titre measles vaccine: better antibody increase from booster dose of the Edmonston–Zagreb vaccine. Vaccine 2001;19:1951–9.

[6] Martins C, Garly ML, Bale C, Rodrigues A, Njie-Jobe J, Benn CS, et al. Measles virus antibody responses in children randomly assigned to receive

standard-titer Edmonston–Zagreb measles vaccine at 4.5 and 9 months of age, 9 months of age, or 9 and 18 months of age. J Infect Dis 2014;210:693–700.

[7] Helfand RF, Witte D, Fowlkes A, Garcia P, Yang C, Fudzulani R, et al. Evaluation of the immune response to a 2-dose measles vaccination schedule administered at 6 and 9 months of age to HIV-infected and HIV-uninfected children in Malawi. J Infect Dis 2008;198:1457–65.

[8] Fowlkes A, Witte D, Beeler J, Audet S, Garcia P, Curns A, et al. Persistence of vaccine-induced measles antibody beyond age 12 months: a comparison of response to one and two doses of Edmonston–Zagreb measles vaccine among HIV-infected and uninfected children in Malawi. J Infect Dis 2011;204(Suppl 1):S149–57.

[9] Scott P, Moss WJ, Gilani Z, Low N. Measles vaccination in HIV-infected children: systematic review and meta-analysis of safety and immunogenicity. J Infect Dis 2011;204(Suppl. 1):S164–78.

[10] Taha TE, Dallabetta GA, Hoover DR, Chiphangwi JD, Mtimavalye LA, Liomba GN, et al. Trends of HIV-1 and sexually transmitted diseases among pregnant and postpartum women in urban Malawi. AIDS 1998;12:197–203.

[11] Cohen BJ, Audet S, Andrews N, Beeler J. Plaque reduction neutralization test for measles antibodies: description of a standardised laboratory method for use in immunogenicity studies of aerosol vaccination. Vaccine 2007;26: 59–66.

[12] Njie-Jobe J, Nyamweya S, Miles DJ, van der Sande M, Zaman S, Touray E, et al. Immunological impact of an additional early measles vaccine in Gambian children: responses to a boost at 3 years. Vaccine 2012;30:2543–50.

[13] Martins CL, Benn CS, Andersen A, Bale C, Schaltz-Buchholzer F, Do VA, et al. A randomized trial of a standard dose of Edmonston–Zagreb measles vaccine given at 4.5 months of age: effect on total hospital admissions. J Infect Dis 2014;209:1731–8.

[14] Aaby P, Martins CL, Garly ML, Bale C, Andersen A, Rodrigues A, et al. Non-specific effects of standard measles vaccine at 4.5 and 9 months of age on childhood mortality: randomised controlled trial. Br Med J 2010;341:c6495.

[15] Markowitz LE, Preblud SR, Fine PE, Orenstein WA. Duration of live measles vaccine-induced immunity. Pediatr Infect Dis J 1990;9:101–10.

[16] Moss WJ, Scott S, Mugala N, Ndhlovu Z, Beeler JA, Audet SA, et al. Immunogenicity of standard-titer measles vaccine in HIV-1-infected and uninfected Zambian children: an observational study. J Infect Dis 2007;196:347–55.

[17] Sutcliffe CG, Moss WJ. Do children infected with HIV receiving HAART need to be revaccinated. Lancet Infect Dis 2010;10:630–42.