SUPPLEMENT ARTICLE

Measles Vaccination in HIV-Infected Children: Systematic Review and Meta-Analysis of Safety and Immunogenicity

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Background. Measles control may be more challenging in regions with a high prevalence of HIV infection. HIV-infected children are likely to derive particular benefit from measles vaccines because of an increased risk of severe illness. However, HIV infection can impair vaccine effectiveness and may increase the risk of serious adverse events after receipt of live vaccines. We conducted a systematic review to assess the safety and immunogenicity of measles vaccine in HIV-infected children.

Methods. The authors searched 8 databases through 12 February 2009 and reference lists. Study selection and data extraction were conducted in duplicate. Meta-analysis was conducted when appropriate.

Results. Thirty-nine studies published from 1987 through 2008 were included. In 19 studies with information about measles vaccine safety, more than half reported no serious adverse events. Among HIV-infected children, 59% (95% confidence intervals [CI], 46–71%) were seropositive after receiving standard-titer measles vaccine at 6 months (1 study), comparable to the proportion of seropositive HIV-infected children vaccinated at 9 (8 studies) and 12 months (10 studies). Among HIV-exposed but uninfected and HIV-unexposed children, the proportion of seropositive children increased with increasing age at vaccination. Fewer HIV-infected children were protected after vaccination at 12 months than HIV-exposed but uninfected children (relative risk, 0.61; 95% CI, .50–.73).

Conclusions. Measles vaccines appear to be safe in HIV-infected children, but the evidence is limited. When the burden of measles is high, measles vaccination at 6 months of age is likely to benefit children of HIV-infected women, regardless of the child's HIV infection status.

Approximately one million HIV-infected children live in the 47 countries with the highest burden of measles [1, 2]. Measles occurs at a younger age and is associated with an increased risk of severe illness and death in HIV-infected children [3, 4]. Measles vaccine, however, has the potential to cause serious adverse events in immunocompromised persons due to replication of measles vaccine virus [5, 6]. Progressive HIV-related immunosuppression can also impair vaccine effectiveness. In healthy immunocompetent persons, adverse events after measles vaccination are usually mild and transient, and seroconversion rates of >90% can be achieved [7, 8].

The World Health Organization (WHO) recommended in 2004 that, unless severely immunocompromised, HIV-infected infants should receive measles vaccine at 6 months of age, followed by another dose at 9 months [8]. In practice, this is difficult to achieve because the child's HIV infection status is usually unknown during early infancy [3]. The WHO Global Advisory Committee on Vaccine Safety (GACVS) subgroup on immune deficiencies commissioned this systematic review and contributed to formulating research questions to reassess current recommendations. The objective was to examine the safety and immunogenicity

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of measles vaccine in HIV-1–infected children to assess the balance of benefits and risks.

METHODS

Information Sources and Search

We searched Medline, Embase, the Cochrane Library, African Index Medicus, the Indian Medlars Centre, Latin American and Caribbean Health Sciences, AIDSLine, and Conference on Retroviruses and Opportunistic Infections abstracts for articles published from the earliest date available through February 2009. We used key words or subject headings for "measles vaccine" or "measles immunization" in combination with "HIV," adapted to each database. We screened bibliographies of selected review articles and contacted experts to identify additional publications or studies. There were no language restrictions.

Eligibility Criteria

Eligible study designs were randomized controlled trials (RCTs) or quasi-RCTs, controlled clinical trials, cohort, case-control, or cross-sectional studies, comparing measles-vaccinated HIV-infected children with measles-vaccinated HIV-uninfected children (either HIV-unexposed or HIV-exposed but uninfected) or HIV-infected children not vaccinated against measles. To assess safety, we also considered case reports that might identify rare adverse events and studies of measles vaccination of HIV-infected children without a comparison group.

The population of interest was children 0–15 years of age, either with confirmed HIV-1 infection or who were exposed to HIV-1 (ie, born to an HIV-1–infected mother) with or without confirmed infection. The intervention was measles vaccination with a licensed, single- or combined-antigen vaccine. Outcomes relating to vaccine safety, immunogenicity, or clinical measles were required to be reported. Studies meeting all criteria were included.

Study Selection

Two reviewers (PS and NL) independently evaluated all retrieved articles sequentially by title, abstract, and full text. Those considered by one or both reviewers to potentially match inclusion criteria were retained at each stage.

Data Collection and Analysis

Two reviewers (PS and ZG) independently extracted data onto piloted structured forms, including information on study population, vaccine types, sample size, loss to follow-up, outcomes, and source of funding. We also extracted information about predefined study characteristics that could result in bias, such as loss to follow-up, lack of blinding in the assessment of outcomes, or differences between groups in the interval between vaccination and serological assessment.

We assessed whether safety outcomes were reported and numbers and types of serious adverse events, including deaths. For measles vaccine immunogenicity, we extracted data on laboratory assays and definitions of serological responses, as well as results. Most studies reported seropositivity after vaccination, but some reported seroconversion (change from seronegative to seropositive or 4-fold increase in titer). We therefore used a composite outcome for serological response, using seropositivity when available and seroconversion otherwise, based on definitions provided by the authors. We considered children to be HIV infected if they met the definition for HIV infection used in the study in which they participated. Data were entered in EpiData (EpiData Association) by each of the reviewers. Discrepancies were resolved by consensus, with a third reviewer (NL) acting as arbiter.

We calculated the percentage seropositive with exact binomial 95% confidence intervals (CIs) separately for each comparison group in each study and displayed these in forest plots. Serological responses in HIV-infected children were compared with those of available comparison groups in each study with use of relative risks (RRs) and 95% CIs. Data were combined, when appropriate, using DerSimonian and Laird random-effects meta-analysis [9]. We quantified between-trial heterogeneity with use of the I^2 statistic [10]. Meta-analysis was considered to be inappropriate when the I^2 statistic exceeded 50% or a single study contributed to $\geq$2 estimates within strata. Between-trial heterogeneity was first explored by stratifying results by age at vaccination (6 months, 9 months, and $\geq$12 months) and then examining heterogeneity within strata. Forest plots of study results were also stratified by serological cutoff point, serological test, interval between vaccination and serology, and receipt of highly active antiretroviral therapy (HAART), and variation between results was assessed visually. Detailed exploration of heterogeneity by meta-regression was not possible because data from 1 study that involved vaccination at different ages [11] would have appeared multiple times. Differences between the results of small and large comparative trials were assessed by visual inspection of funnel plots and with a statistical test for asymmetry [12] for outcomes reported by $\geq$10 trials. Analyses were conducted using Stata, version 10 (StataCorp). The study protocol, search strategy, and criteria for the assessment of the risk of bias are available on request from the authors.

RESULTS

Description of Studies Included

The searches identified 723 potentially relevant articles (Figure 1). Most ineligible studies were excluded on the basis of information in the title or abstract. We included 39 articles published from 1989 through 2008 in the review (Table 1). There were 23 articles with comparison groups that reported data from 25 separate study populations. All reported on immunogenicity [11, 13,

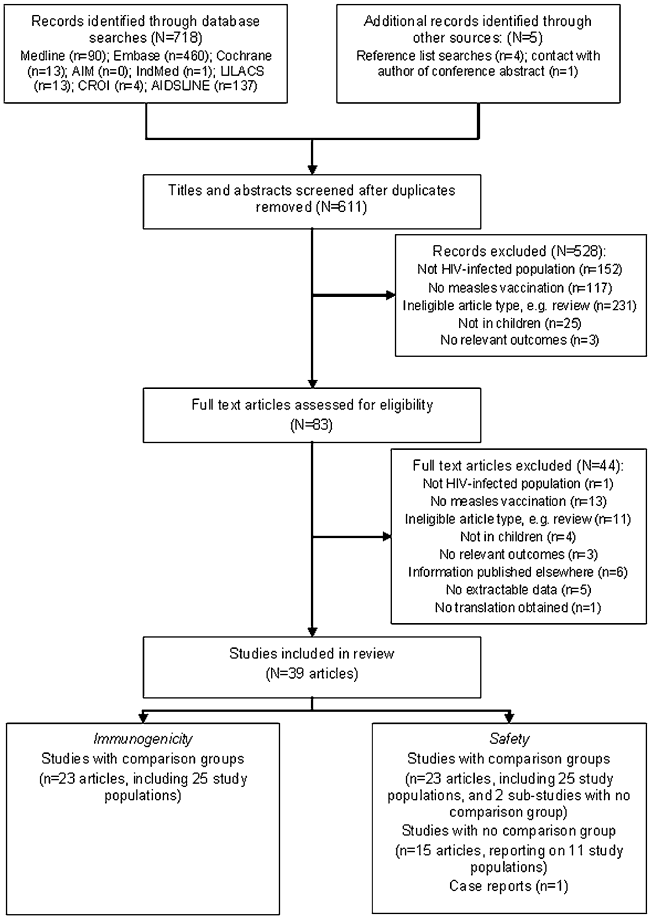

Figure 1. Flow Chart of Study Selection. AIM, African Index Medicus; CROI, Conference on Retroviruses and Opportunistic Infections; IndMed, Indian Medlars Centre; LILACs, Latin American and Caribbean Health Sciences.

19–25, 29–33, 36, 37, 39, 42, 45–49], and 10 (11 study populations) reported on adverse events [11, 23, 24, 25, 30, 36, 37, 39, 42, 47] (Figure 1). In total, 4520 children in comparative studies were vaccinated against measles. Of these, 716 were HIV infected, 1312 were HIV exposed but uninfected, and 1632 were HIV unexposed. There were 860 vaccinated children in 2 studies in which the numbers vaccinated in each comparison group were not provided [23, 39]. Twenty-three studies were available for examining the comparison of serological responses in measles-vaccinated HIV-infected children with measles-vaccinated HIV-uninfected children (either HIV unexposed or HIV exposed but uninfected) [11, 13, 20, 21, 23–25, 29–33, 36, 37, 39, 42, 45–49]. Two of these studies also included a comparison between measles-vaccinated HIV-infected children and HIV-infected children either not vaccinated or not revaccinated against measles [29, 36]. In addition, 1 study restricted to HIV-infected children compared vaccination at 6 and 12 months with vaccination at 12 months only [22], and 1 study compared seroconversion in HIV-infected children receiving or not receiving HAART [19].

Noncomparative studies examining only HIV-infected children were included in the assessment of measles vaccine safety (Figure 1). We included 15 articles (reporting data from 11 studies) published from 1987 thtough 2008 [14–18, 26–28, 34, 35, 38, 40, 41, 43, 44] and data reported from 2 of the comparative studies that involved prospective revaccination of only HIV-infected children (referred to as substudies) [33, 45]. These 13 studies involved at least 515 measles-vaccinated HIV-infected children [14, 16– 18, 26 27, 33– 35 38 40 43 45], because the number vaccinated was unclear in 2 studies [40, 43]. We also included a case report of a child in the United Kingdom in the assessment of measles vaccine safety only [6].

Potential for Bias

There were 7 prospective cohort studies [11, 23, 29, 30, 37, 39, 47], 12 cross-sectional or retrospective cohort studies [13, 19, 20, 24, 31–33, 36, 45, 46, 48,49], and 1 RCT [22]. The study design in 5 studies (reported in 3 articles) was not clear [21, 25, 42]. In prospective studies and the RCT, 44%–100% of vaccinated children contributed to the immunogenicity analyses, with >75% contributing in 5 studies [11, 22, 29, 37, 47]. Only 3 of 25 studies reported blinding in the assessment of outcomes related to either the children's HIV infection or vaccination status [23, 30, 31]. The interval between vaccination and serological assessment was reported to be similar between groups in only 2 studies [31, 48]; in 7 studies, the interval was not reported but was likely to be similar [11, 23, 29, 30, 42, 45, 47]. Details of all items assessed can be seen in Supplementary Table 1.

Smaller trials tended to show lower serological responses than larger trials in HIV-infected children, compared with HIV-exposed but uninfected children ($P = .015$ from test for funnel plot asymmetry in the only comparison containing >10 trials). This finding persisted in studies in which children were vaccinated at 9 months (8 studies; $P = .019$) but not in which children were vaccinated at 6 months (3 studies; $P = .308$) or ≥12 months (5 studies; $P = .442$) of age.

Measles Vaccine Safety

More than 1200 HIV-infected measles-vaccinated children were included in 39 comparative and noncomparative studies assessed for adverse events (number unclear in 6 studies [23, 25, 32, 39, 40, 43]). We did not identify any study that explicitly reported measles inclusion body encephalitis, giant cell pneumonia, or thrombocytopenia in an HIV-infected child. Only 19 studies, involving at least 630 children, made explicit reference to adverse events (Table 2). In 7 studies, there was an explicit statement about the absence of adverse events in HIV-infected children [17, 24, 25, 26, 27, 33, 38]. Seven studies had similar statements but also reported results that made interpretation difficult (eg, that hospitalizations or deaths occurred among study children) [23, 30, 36, 40, 42, 47]. The remaining 5 studies reported that deaths or other serious adverse events occurred among study children [6, 11, 34, 37, 39].

Table 1. Description of Characteristics of Included Studies

Study	Study design	Country	Study setting and population	Age at last vaccination (HIV-infected)	Vaccine used	Groups examined[a]	Outcomes reported	Number measles vaccinated	Interval between vaccination and serology (HIV-infected)
Al-Attar 1995 [13]	Cross-sect./ retrospective cohort	USA	Children at HIV clinic, mothers HIV-positive or high risk of being HIV-infected	1.2–2.3yr (median 1.33yr)	Strain NR, preparation NR	1,3,4[b]	S_0 I_4 I_5 M_1	56	1mo–6.7yr (mean 1.6yr)
Arpadi 1996 [14] (& Arpadi 1992 [15])	Cross-sectional	USA	Perinatally HIV-infected children, 9-168mo at time of study	Unclear. Min. age at first dose 6mo (median 14mo)	Strain NR, monovalent and MMR used	1	S_0 P_1 I_0 M_0	81	NA
Aurpibul 2006 [16]	Cross-sectional	Thailand	Children on HAART, >5yr, CD4>15% after immunosuppression below this, unclear if vaccinated before or while on HAART	Unclear	Strain NR, preparation NR	1	S_0 I_0 M_0	85	NA
Aurpibul 2007 [17]	Prospective cohort	Thailand	Children on HAART, >5yr, CD4>15%, measles seronegative	Assume around age tested negative in previous study: mean 9.9yrs (SD 2.7yr)	Schwarz, MMR	1	S_1 S_2 P_1 I_0 M_0	51	NA
Bekker 2006 [18]	Prospective cohort	Netherlands	Children on HAART, <18yr	First dose, n=3: approx. 14mo Revaccination, n=15: median 7.3yr (IQR 4.2–9.0yr)	Strain NR, MMR	1	S_0 I_0 M_0	18	NA
Berkelhamer 2001 [19]	Cross-sect./ retrospective cohort	USA	Children's hospital, perinatally HIV-infected <12yr, untreated, non-HAART or HAART regimens	3.9–11yr (mean 7.1yr)	Strain NR, MMR	1,4[c]	S_0 I_2 M_1	28	HAART: 1–4mo (median 2mo) No HAART: 1–9mo (median 3mo)
Breña 1993 [20]	Cross-sect./ retrospective cohort	USA	Hospital pediatric HIV program	1.2–3yr (median 1.3yr)	Strain NR, MMR	1,3	S_0 I_1 I_5 M_1	33	1mo–3.5yr (median 2mo)
Brunell 1995a [21]	Unclear	USA	Perinatally HIV-infected infants; source of controls unclear	Min. 1.2yr	Strain NR, MMR (MMRV in some controls)	1,2	S_0 I_1 I_5 M_0	30	2mo–2.3yr (median 7mo)
Brunell 1995b [21]	Unclear	USA	Children 1.5–9yr; source unclear	0.7–2.2yr (median 1.3 yr)	Strain NR, MMR	1,2	S_0 I_5 M_1	66	.75mo–10.6yr (median 2.4yr)

Table 1. (Continued)

Study	Study design	Country	Study setting and population	Age at last vaccination (HIV-infected)	Vaccine used	Groups examined[a]	Outcomes reported	Number measles vaccinated	Interval between vaccination and serology (HIV-infected)
Chandwani 1998 [22]	RCT	Unclear	Infants born to HIV-infected mothers	Approx. 1yr	Strain NR, preparation NR	1,4[d]	S_0 P_1 I_4 M_0	110	Approx. 1.5mo
Cutts 1993 [23]	Prospective cohort	Zaire	Perinatal HIV transmission study, infants born to HIV-infected or -uninfected mothers	Approx. 6mo (mean 0.5yr, all groups)	High-titer E-Z, monovalent	1,2,3	S_1 S_2 S_3 I_3 M_1	475	Approx. 3mo
Echeverria Lecuona 1996 [24]	Cross-sect./ retrospective cohort	Spain	Infants of HIV-infected mothers born and followed up at study hospital	Approx 1yr	Strain NR,MMR	1,3	S_1 S_2* P_1 I_1 M_0	40	Approx. 1–2yr
Embree 1989 [25]	Unclear	Kenya	Perinatal HIV transmission study	Unclear	Strain NR, preparation NR	1,3	S_1 S_2* I_4 M_1	159	Unclear
Fernandez-Ibieta 2007 [26]	Retrospective cohort	Spain	Immune-deficiency unit, children 1.5–19yr	Unclear	Strain NR, MMR	1	S_1 S_2* I_0 M_0	55	NA
Frenkel 1994 [27] (& Frenkel 1992 [28])	Cross-sectional & prospective cohort	USA	Children 1.4–12yr, 80% on ART, HIV-infected and symptomatic	Unclear	Strain NR, MMR	1	S_1 S_2* I_0 M_0	10	NA
Goon 2001 [6]	Case report	UK	HIV-infected child	14mo	Edmonston strain, MMR	1	S_1 S_2 S_3 I_0 M_1	1	NA
Helfand 2008 [11]	Prospective cohort	Malawi	Health center, children attending for routine 14 week immunization visits	Approx. 9mo	E–Z, monovalent	1,2,3	S_1 S_2 S_3 I_1 M_0	857 included (1444 total)	Approx. 3mo
Hilgartner 2001 [29]	Prospective cohort	USA	Cohort study, hemophiliac children	Min. 6mo	Strain NR, preparation NR	1,2,4[e]	S_0 P_1 I_5 M_0	34	Approx. 3–9mo
Lepage 1992 [30]	Prospective cohort	Rwanda	Infants of HIV-infected or HIV-uninfected mothers	.48–.84yr (median .51yr)	High-titer, E–Z, monovalent	1,2,3	S_1 S_2 S_3 I_1 I_3 I_5 M_1	372	Approx. 3mo
Lindgren-Alves 2001 [31]	Cross-sect./ retrospective cohort	Brazil	HIV centre, perinatally infected children; teaching hospital controls	Unclear	Strain NR, preparation NR	1,2	S_0 I_4 I_5 M_0	50	median 1.4yr, mean 2.45yr (SD 2.6yr)
Lyamuya 1995 [32]	Cross-sect./ retrospective cohort	Tanzania	Children at mother and child health clinics	Min. all groups .25yr (median .75yr)	Schwarz, preparation NR	1,3	S_0 I_4 I_5 M_0	NR	Unclear, tested at up to 5yr
Marczynska 2001 [33]	Cross-sect./ retrospective cohort	Poland	Medical university, HIV-infected children on HAART; HIV-uninfected comparison group, unclear	Unclear	Schwarz, both monovalent and MMR used	1,2	S_0 I_1 M_0	38	3mo–13yr (mean 3.1yr)

Table 1. (Continued)

Marczynska 2001 [33] (substudy)	Prospective cohort	Poland	Children revaccinated if measles antibody negative	5–8yr	Schwarz, MMR	1	$S_1\ S_2{*}\ I_0\ M_0$	9	NA
McLaughlin 1988 [34]	Retrospective cohort	USA	Children <12yr, vaccinated before HIV diagnosis	Unclear	Strain NR, both monovalent and MMR used	1	$S_1\ S_2\ S_3\ I_0\ M_0$	70	NA
Melvin 2003 [35]	Retrospective cohort	USA	Children perinatally HIV-infected; 1st dose before HAART, revaccination on HAART	3–14yr (median 7yr)	Edmonston strain, MMR	1	$S_0\ I_0\ M_0$	18	NA
Molyneaux 1993 [36]	Cross-sect./ retrospective cohort	UK	Perinatal HIV transmission study	Min. 1yr	Strain NR, both monovalent and MMR used	1,3,4[f]	$S_1\ S_2\ I_1\ M_0$	70	Approx. 3–9mo
Moss 2007 [37]	Prospective cohort	Zambia	Infants attending a public health care facility	Approx. 9mo	E–Z, preparation NR	1,2,3	$S_1\ S_2\ S_3\ I_1\ I_3\ I_5\ M_1$	441	Approx. 1–6mo
Ndikyeze 1987 [38]	Cross-sectional	Rwanda	Children 8–19mo	HIV vaccinated before 12mo	Strain NR, preparation NR	1	$S_1\ S_2{*}\ I_0\ M_0$	3	NA
Oxtoby 1989 [39]	Prospective cohort	Zaire	Infants with HIV-infected or -uninfected mothers	Approx. 9mo	Strain NR, preparation NR	1,2,3	$S_1\ S_2\ S_3\ I_2\ M_0$	954	Approx. 1yr
Palumbo 1992 [40] (& Hoyt 1992 [41])	Prospective cohort and retrospective case-finding	USA	Children approximately 1–10yr	Unclear	Edmonston strain, MMR	1	$S_1\ S_2\ S_3\ I_0\ M_1$	92	NA
Rudy 1994a [42]	Unclear	USA	Special immunology clinic, infants vaccinated at <12mo	6mo–1yr	Strain NR, monovalent	1,3	$S_1\ S_2\ I_4\ M_0$	35	Approx. 1–3mo
Rudy 1994b [42]	Unclear	USA	Special immunology clinic, children vaccinated at >12mo	1yr–1.3yr	Strain NR, MMR	1,3	$S_1\ S_2\ I_4\ M_0$	26	Approx. 1–3mo
Ruel 2008 [43] (& Ruel 2007 [44])	Prospective cohort	Uganda	Children 1–10y, unclear if ART	Unclear	Strain NR, preparation NR	1	$S_0\ P_1\ I_0\ M_0$	11	NA
Takano 2003 [45]	Cross-sect./ retrospective cohort	Brazil	Pediatric AIDS clinic	Min. 1yr	Strain NR, MMR	1,2	$S_0\ I_5\ M_0$	139	Approx. 1–3mo
Takano 2003 [45] (substudy)	Prospective cohort	Brazil	Children without protective measles antibody, all on HAART	Unclear	Strain NR, MMR	1	$S_0\ I_0\ M_0$	12	NA
Tejiokem 2007 [46]	Cross-sect./ retrospective cohort	Cameroon, CAR	4 pediatric care centers, infants with HIV-infected mothers	9mo–1.3yr	Strain NR, preparation NR	1,3	$S_0\ I_1\ I_5\ M_0$	127	3.9mo–2.6yr (median 1.4yr, all)

Table 1. (Continued)

Study	Study design	Country	Study setting and population	Age at last vaccination (HIV-infected)	Vaccine used	Groups examined[a]	Outcomes reported	Number measles vaccinated	Interval between vaccination and serology (HIV-infected)
Thaithumyanon 2000 [47]	Prospective cohort	Thailand	Infants of HIV-infected mothers	Approx. 9mo	Schwarz, monovalent	1,3	S_1 S_2 S_3 I_2 I_5 M_1	33	Approx. 3mo
Waibale 1999 [48]	Cross-sect./retrospective cohort	Uganda	Pediatric clinic and pediatric HIV clinic, infants	6mo–2.2yr (median 0.8yr)	Strain NR, monovalent	1,3	S_0 I_1 I_5 M_0	243	2.7mo–2.4yr (median 14mo)
Walter 1994 [49]	Cross-sect./retrospective cohort	USA	Pediatric infectious disease clinic, HIV-infected or child of HIV-infected mother	Mean 1.7yr	Strain NR, MMR	1,3	S_0 I_4 I_5 M_0	104	Mean 3.1mo

NOTE. CAR, Central African Republic; mo, months of age; Max, maximum; Min, minimum; MMR, measles, mumps, rubella vaccine; MMRV, measles, mumps, rubella, varicella vaccine; NA, not applicable; NR, not reported; yr, years of age;

[a] Groups: 1, HIV-infected (vaccinated); 2, HIV-unexposed (vaccinated); 3, HIV-exposed but uninfected (vaccinated); 4, other;

[b] ''other'' group in Al-Attar et al are HIV-infected children, infected via transfusion (group 1 are HIV-infected by vertical transmission);

[c] ''other'' group in Berkelhamer et al are HIV infected children not on HAART (group 1 are HIV-infected on HAART for ≥ 4 months prior to vaccination);

[d] ''other'' group in Chandwani et al are HIV-infected vaccinated at 12 months only (group 1 are HIV-infected, vaccinated at 6 and 12 months);

[e] ''other'' group in Hilgartner et al are HIV-infected but unvaccinated (group 1 are HIV-infected, vaccinated);

[f] ''other'' group in Molyneaux et al are HIV-infected but unvaccinated (group 1 are HIV-infected, vaccinated);

S Safety outcomes: S_0, no adverse event information reported; S_1, explicit reporting on adverse events; S_2, explicit reporting on serious adverse events; S_2*, information based on 'adverse event statement'; S_3, information on deaths reported;

P Progression of HIV: P_1, information on progression of HIV-related disease reported;

I Immunogenicity outcomes: I_0, immunogenicity either not reported or not assessed in this review; I_1, seropositivity after vaccination reported; I_2, seroconversion (seronegative before vaccination, seropositive after) reported; I_3, seroconversion (4-fold rise in titer) reported; I_4, measure which might either be seropositivity after vaccination or seroconversion (seronegative before vaccination, seropositive after) is reported; I_5 summary immunological measure (e.g. geometric mean titer) reported for each group;

M Measles outcomes: M_0, no information on occurrence of clinical measles, or unclear when or in which group clinical measles occurred; M_1, reports explicitly on clinical measles after vaccination and numbers given by group.

Deaths after vaccination were reported in 7 studies [11, 23, 30, 34, 37, 40, 47]. No study stated that any deaths were related to measles vaccination. In 1 study, it was stated that "no excess of…death was found in association with vaccination" [39, p31]. The child described in the case report survived [6]. At least 75 deaths were reported among vaccinated HIV-infected children (in 1 study, the number reported included unvaccinated children).

Details about hospitalizations were infrequently reported, although 2 large prospective studies involving 1298 vaccinated children reported that no hospitalizations were considered to be measles vaccine related [11, 37]. One study reported a retrospective search for adverse events in the study cohort of 221 vaccinated children [34]. No serious adverse events were documented, and no cases of measles vaccine–related encephalitis were reported to the regional authority during the period under review. We found no studies directly comparing hospitalization rates in vaccinated and unvaccinated HIV-infected children. There was only 1 report of a serious adverse event potentially associated with measles vaccination in which receipt of measles vaccine could be confirmed. This was a nonfatal illness resembling measles after vaccination of a 14-month-old boy, in whom measles vaccine virus was sequenced from a peripheral blood sample [6].

Measles Vaccine Immunogenicity

The majority of studies used enzyme-linked immunoassays to determine measles antibody levels, but definitions and cutoff points varied across studies (Figures 2–4). Two studies used high-titer Edmonston-Zagreb vaccine, defined as potencies >4.7 $\log_{10}$ in children vaccinated at 6 months of age [23, 30]. These studies were included, but we did not combine these results with those from studies using standard-titer measles vaccine.

HIV-Infected Children. Levels of serological response among HIV-infected children varied between studies, but there was no clear pattern according to age at primary vaccination (Figure 2). One study examined vaccination with standard-titer measles vaccine at 6 and 9 months of age [11]; 59% (95% CI, 46%–71%) of children were seropositive after measles vaccination at 6 month of age, and 64% (95% CI, 49%–78%) were seropositive after measles vaccination at 9 months of age. These findings were consistent with results from 6 of 7 other studies of HIV-infected children receiving primary measles vaccination at 9 months of age. After vaccination at ≥12 months of age, point estimates ranged from 21% to 100%. No single factor (eg, serological cutoff point, serological test used, and interval between vaccination and serology or receipt of HAART) appeared to account for the variation between studies of vaccination at 9 or 12 months of age.

HIV-Exposed but Uninfected Children. Seropositivity after vaccination with standard-titer measles vaccine at 6 months was 68% (95% CI, 62%–74%) [11]. After vaccination at 9 months of age, point estimates of the proportion of seropositive children ranged from 62% to 100% and were ≥90% in 4 of 8 studies (Figure 3). After vaccination at 12 months of age, the proportion of seropositive HIV-exposed but uninfected children was >90% in all studies.

HIV-Unexposed Children. The pattern of serological response by age at measles vaccination in HIV-unexposed children was similar to that observed among HIV-exposed but uninfected children (Figures 3 and 4). Nine studies included a comparison group of HIV-unexposed children (Figure 4). In the only study using standard-titer measles vaccine at 6 months of age, 62% (95% CI, 57%–66%) of children became seropositive [11]. The proportion of seropositive children was higher after measles vaccination at 9 months and was 100% after vaccination at 12 months in 2 small studies.

Comparisons Between Groups, According to HIV Infection Status

In the only study using standard-titer measles vaccine at 6 months of age [11], there was no statistical evidence of a difference in serological response rates between HIV-infected and children who were either HIV-exposed but uninfected or HIV-unexposed (Table 3).

There were 2 studies that examined the effects of high-titer measles vaccine given at 6 months of age [23, 30]. In HIV-infected children in these studies, serological responses were slightly higher than those in the study that used standard-titer vaccine [11] (Figure 2). In comparative analyses, the serological response after vaccination with standard-titer vaccine at 6 months of age in HIV-exposed but uninfected children was slightly greater than in HIV-unexposed children (RR, 1.11; 95% CI, .99–1.24) [11], with similar results in high-titer studies [23, 30].

After vaccination at 9 months, serological responses in HIV-exposed but uninfected and HIV-unexposed groups were similar (Table 3). Comparisons between HIV-infected and HIV-exposed but uninfected children showed lower levels of seropositivity in HIV-infected children at 12 months (RR, 0.61; 95% CI, .50–.73) [11]. No studies of children vaccinated at ≥12 months of age reported a comparison between HIV-exposed but uninfected and HIV-unexposed children.

Comparisons Between HIV-Infected Children, According to Antiretroviral Therapy

We found 2 studies that assessed the impact of antiretroviral therapy on serological responses to measles vaccine. Berkelhamer et al [19] examined HIV-infected children who had previously received measles vaccine but had nonprotective antibody levels. Seroconversion after revaccination was compared between 14 children receiving HAART and 14 children who were not receiving HAART (data from untreated children and those receiving less potent regimens combined by authors). More children seroconverted who were receiving HAART than

Table 2. Information About Deaths and Serious Adverse Events in Studies Where These Outcomes Are Reported

Study	Measles vaccinated HIV-infected children, *n*	Post-vaccination deaths in HIV-infected children, *n*	Time observed for deaths	Follow up for deaths, *n* (% lost to follow up)	Deaths reported to be related to vaccination by investigators,[a] *n*	Post-vaccination SAE (other than death) in HIV-infected children, *n*	Time observed for SAE	Follow up for SAE other than death, *n* (% lost to follow up)	SAE reported to be related to vaccination by investigators, *n*[a]
Aurpibul 2007 [17]	51	NR	-	-	-	0	Unclear, 4 weeks?	51 (0%)	0
Cutts 1993 [23]	Unclear, 49 in safety data, 34 in immunogenicity data	9	Median 1.7 years	NR (NR%)	NR	0	5-15 days	49 (NR%)	NA
Echeverria Lecuona 1996 [24]	10	NR	-	-	-	0	NR	10 (NR%)	0
Embree 1989 [25]	Unclear, 61 children of HIV infected mothers	NR	-	-	-	0	NR	61 (NR%)	NA
Fernandez-Ibieta 2007 [26]	55	NR	-	-	-	0	NR	55 (NR%)	NA
Frenkel 1 994 [27] (& Frenkel 1992 [28])	10	NR	-	-	-	0		10 (NR%)	NA
Goon 2001 [6]	1	0	1 year	1 (0%)	NA	1	1 year	1 (0%)	1
Helfand 2008 [11]	84	20	6 months	84 (19%[b])	0	NER	4 weeks	83 (NR%)	0
Lepage 1992 [30]	43	15	18 months	43 (NR%)	0	0	18 months	43 (NR%) 43 (16%)	NA
Marczynska 2001 [33] (substudy)	9	NR, but all present at end of follow up	3 months	9 (0%)	NA	0	3 months	9 (0%)	NA
McLaughlin 1988 [34]	70	Unclear, 41 deaths amongst 221 measles vaccinated or unvaccinated children	NR	70 (NR%)	NR	1 possible, but vaccination not confirmed	NR	70 (NR%)	1 possible, but vaccination not confirmed
Molyneaux 1993 [36]	9	NR	-	-	-	NER, 1 where unclear if after vaccination	NR	9 (NR%)	NR

Table 2. (Continued)

Moss 2007 [37]	66	28	27 months	66 (27.3%[c])	''not known''	≥ 1 (only given as hospitalization for measles-like rash)	4 weeks	66 (<11%[d])	NR
Ndikyeze 1987 [38]	3	NR, but all followed up	NR	3 (0%)	NA	0	NR	3 (0%)	NA
Oxtoby 1989 [39]	Unclear, 37 in immunogenicity data	NER	NR	NR (NR%)	NR	NER	NR	NR (NR%)	NR
Palumbo 1992 [40] (& Hoyt 1992 [41])	92 vaccinated during outbreak, unknown number in case finding	NR for outbreak, 2 in case finding [e]	NR	NR (NR%)	NR	0	NR	NR (NR%)	NA
Rudy 1994a&b [42]	13 (a) 12 (b)	NR	-	-	-	0	NR	13 (a) (NR%) 12 (b) (NR%)	NA
Thaithumyanon 2000 [47]	16	1	12 weeks	16 (6.25%[f])	0	0	''short term''	16 (NR%)	NA

NOTE. Included studies which are not listed in this table did not make any report on the occurrence or non-occurrence of deaths or Serious Adverse Events

NR, not reported; NER, not explicitly reported, only a vague statement made (e.g. ''We did not find any increase in serious adverse events among HIV-infected children''); NA, not applicable;

[a] numbers quoted relate to explicit statements

[b] based on 16 moved or withdrawn

[c] based on 18 moved, withdrawn or status unknown

[d] based on 7 moved or withdrawn at 1-6 months

[e] vaccinated 26 and 28m before measles

[f] based on 1 not completing

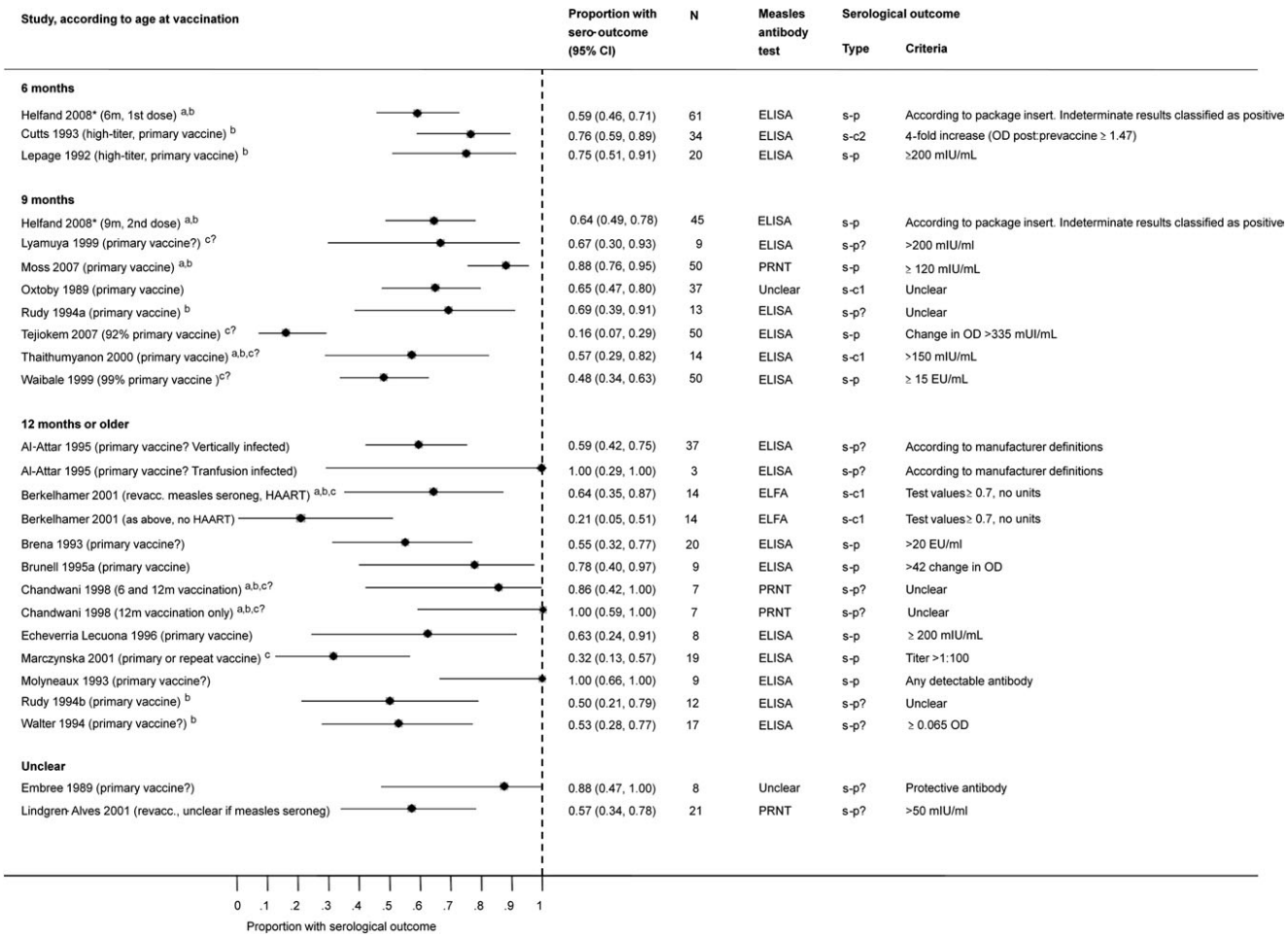

Figure 2. Seropositivity or seroconversion after measles vaccination in HIV-infected children, absolute values, all studies. *Results are from the same study after vaccination at 6 and 9 months of age; s-p, seropositivity; s-p?, unclear if those seropositive prior to vaccination are excluded; s-c1, seroconversion from negative to positive; s-c2, seroconversion with 4-fold rise in titer; OD, optical density; change in OD, delta optical density ((mean of 2 viral antigen determinations - mean of 2 controls) x 1000); EU, ELISA units. [a] Studies where more than 75% of vaccinated children were available for immunogenicity analyses [b] Studies where blood was drawn for measles serology less than 6 months after vaccination [c] Studies where children received highly active antiretroviral therapy (HAART) [c?] Studies where it is not clear if children received HAART

those not receiving HAART (RR, 3.00; 95% CI, 1.02–8.80) despite being slightly older and having more advanced HIV disease. Marczynska et al [33] compared 19 HIV-infected children receiving HAART (mean age, 5.4 years) with 19 HIV-unexposed children (mean age, 6 years). The seropositivity rate was lower in revaccinated HIV-infected children than in HIV-unexposed children (RR, 0.33; 95% CI, .18–.63).

DISCUSSION

This systematic review synthesized published evidence about the safety and immunogenicity of measles vaccine in 39 studies involving >1200 HIV-infected children. No study reported deaths in HIV-infected children related to measles vaccine, and we found only 1 case report of a serious adverse event possibly related to measles vaccination. There was an absence of studies directly comparing vaccinated with unvaccinated HIV-infected children. Seropositivity after vaccination in HIV-infected children did not improve as age at vaccination increased, unlike in HIV-uninfected children.

The main strengths of our review were the systematic strategy and broad search terms used to identify studies in a wide range of databases and the rigorous methods used to extract and appraise the data. The main limitation of this review was the need to rely on observational data, apart from a small uncompleted RCT [22]. The potential for confounding and bias should therefore be considered when interpreting the results. There was some statistical evidence that smaller trials were more likely to show lower serological responses in HIV-infected children, compared with HIV-exposed but uninfected children, which could result from publication bias [12]. There might also be systematic differences between smaller and larger trials. Trials of children vaccinated at older ages tended to be smaller, and the funnel plot asymmetry persisted in the group of trials among

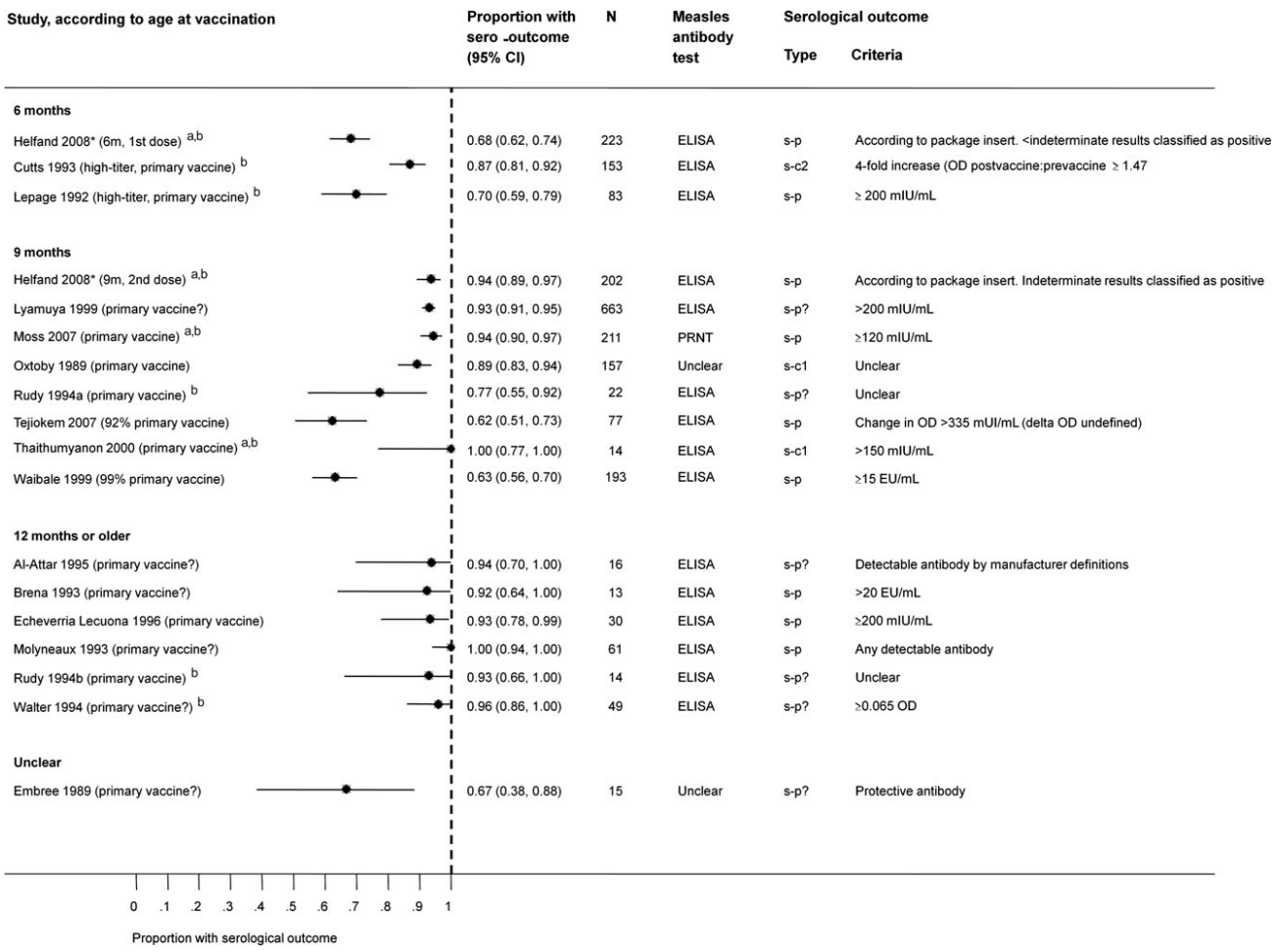

Figure 3. Seropositivity or Seroconversion after Measles Vaccination in HIV-Exposed but Uninfected Children, Absolute Values, All Studies.* Results are from the same study after vaccination at 6 and 9 months of age; s-p, seropositivity; s-p?, unclear if those seropositive prior to vaccination are excluded; s-c1, seroconversion from negative to positive; s-c2, seroconversion with 4-fold rise in titer; OD, optical density; change in OD, delta optical density ((mean of 2 viral antigen determinations - mean of 2 controls) × 1000); EU, ELISA units. [a] Studies where more than 75% of vaccinated children were available for immunogenicity analyses [b] Studies where blood was drawn for measles serology less than 6 months after vaccination

children vaccinated at 9 months but not at 12 months. Differences in types of serological assay and definitions of protective levels were likely to affect the proportion of children seropositive after vaccination in the HIV-infected group. We could not assess these differences formally because of variability in the assays.

We did not find evidence that serious adverse events due to measles vaccination of HIV-infected children were common in studies reporting this outcome. Generally poor reporting of safety outcomes meant, however, that the incidence of adverse events could not be estimated with confidence. Furthermore, the sample sizes of prospective studies were insufficient to detect rare events. The lack of studies directly comparing vaccinated with unvaccinated HIV-infected children limited assessment of whether adverse events occurring after vaccination were in excess of the illnesses and deaths that would have occurred if these children had not been vaccinated. We identified a case report of a 14-month-old, HIV-infected boy who developed fever and rash after receiving measles-mumps-rubella vaccine that resolved after hospitalization without complications [6]; however, up to 5% of healthy individuals may experience fever after measles vaccination and 2% may have a rash [3]. The only documented case of fatal disease associated with measles vaccine virus in an HIV-1-infected person was in a 20-year-old man in the United States who died 15 months after receiving his second dose of measles vaccine [5]. Ten months after measles vaccination, he developed a giant cell pneumonia and measles vaccine virus was identified in his lung.

In areas where measles virus is circulating [1], HIV-infected and HIV-exposed but uninfected children could benefit from earlier vaccination. Children born to HIV-infected women become susceptible to measles virus infection at a younger age than do children of uninfected mothers [3], because placental transfer of maternal antibodies is impaired in HIV-1–infected women

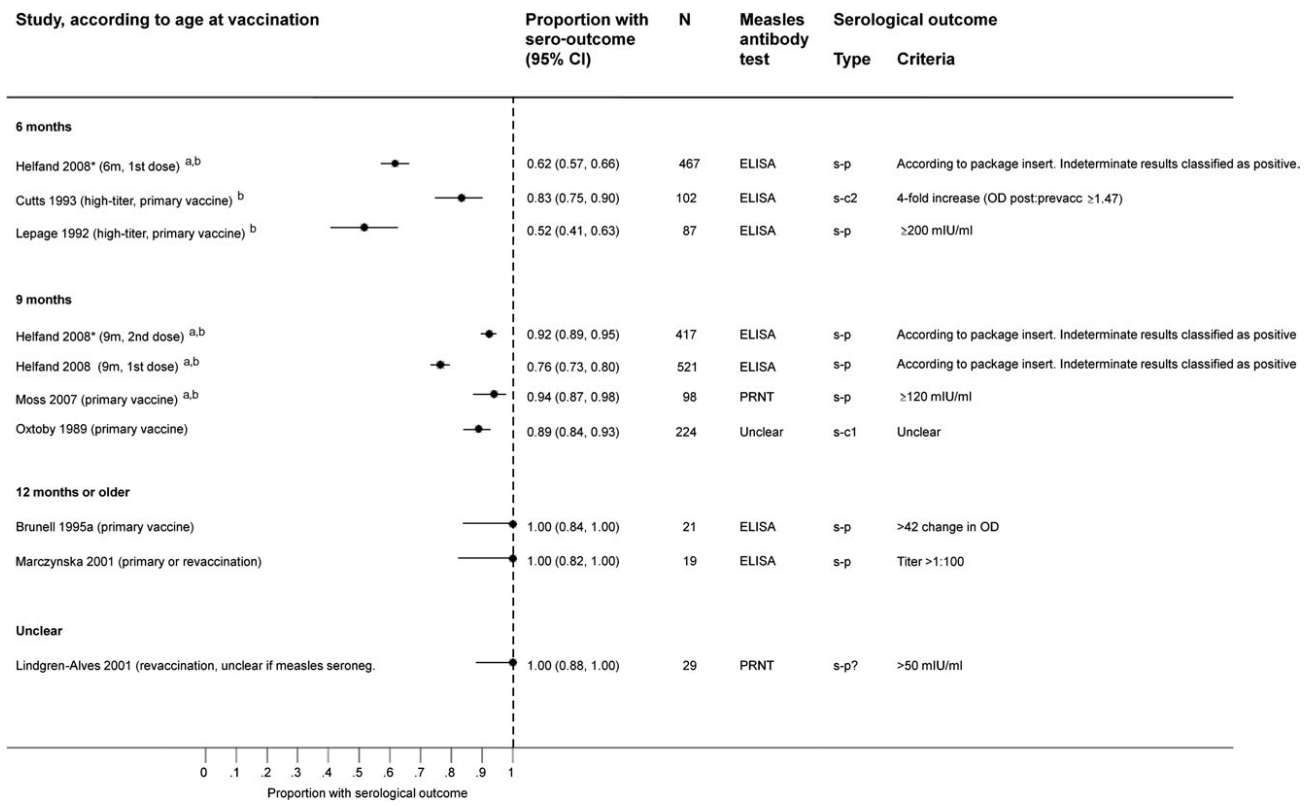

Figure 4. Seropositivity or Seroconversion after Measles Vaccination in HIV-Unexposed Children, Absolute Values, All Studies. * Results are from the same study after vaccination at 6 and 9 months of age; s-p, seropositivity; s-p?, unclear if those seropositive prior to vaccination are excluded; s-c1, seroconversion from negative to positive; s-c2, seroconversion with 4-fold rise in titer; OD, optical density; change in OD, delta optical density ((mean of 2 viral antigen determinations - mean of 2 controls) × 1000); EU, ELISA units. [a] Studies where more than 75% of vaccinated children were available for immunogenicity analyses [b] Studies where blood was drawn for measles serology less than 6 months after vaccination

[50]. Our findings suggest that measles vaccine could be given to all infants of HIV-infected mothers at 6 months, even if the child's HIV infection status is not known. Although only 1 study used standard-titer measles vaccine at this age, it was a large well-conducted prospective study [11]. Two studies using high-titer measles vaccine at 6 months of age produced results consistent with this pattern [23, 30]. Although this vaccine is no longer used, these studies provide supportive evidence of the immunogenicity of early measles vaccination in HIV-infected children. The level of seropositivity in HIV-infected children vaccinated at 6 months of age was comparable to that achieved in HIV-infected children receiving primary measles vaccination at 9 months in several other studies [32, 39, 42, 47]. In addition, the response to measles vaccine at 6 months among HIV-exposed but uninfected children was slightly higher than that in HIV-unexposed children [11]. Lower levels of maternal antibody in HIV-exposed but uninfected children [50] might allow for a better immunological response to earlier doses of measles vaccine.

The results of this review have implications for measles control strategies in areas with a high prevalence of HIV infection. The 2009 WHO position paper on measles vaccination, supported by the results of this review, now states that the first dose of measles vaccine can be given as early as 6 months in areas where there is a high incidence of both measles and HIV infection [7]. This recommendation means that HIV infection status does not have to be known before early vaccination. There are opportunities to provide measles vaccine at 6 and 9 months to children of mothers who are known to be HIV infected and are receiving care in Prevention of Mother-To-Child Transmission Plus or antiretroviral treatment programs. Supplementary immunization activities and programs to accelerate coverage of routine measles vaccination would also increase levels of indirect protection to susceptible HIV-infected children. There are some priorities for both public health research and practice. Large studies of the effects of expanded access to HAART on susceptibility to measles and serological responses to measles vaccination should be conducted, and the assessment and reporting of measles vaccine safety need to be improved. In summary, measles vaccines appear to be safe in HIV-infected children, but evidence is limited. Because of the potentially increased case-fatality associated with measles in HIV-infected children, children of HIV-infected mothers may benefit from initial vaccination at 6 months in regions with high measles burden, regardless of the child's HIV status.

Table 3. Comparative Immunogenicity of Standard-Titer Measles Vaccine, According to HIV Status

Age at vaccination	Studies, n	Group 1, n	Group 2, n	Heterogeneity I^2, %	Relative risk (95% CI)[a]
		HIV-infected	HIV-unexposed		
6 months	1[b]	61	467	NA	0.96 (.77–1.19)
9 months	3	132	417	81.5	NA
12 months	2	28	40	84.8	NA
		HIV-infected	HIV-exposed, uninfected		
6 months	1[b]	61	223	NA	0.87 (.69–1.09)
9 months	8	268	1539	79.6	NA
12 months	6	103	183	0.0	0.61 (.50–.73)
		HIV-exposed, uninfected	HIV-unexposed		
6 months	1[b]	223	467	NA	1.11 (.99–1.24)
9 months	3	570	739	0.0	1.01 (.98–1.04)
12 months	0	NA	NA	NA	NA

NOTE. NA, not applicable

[a] Derived from random effects meta-analysis for strata with more than one study

[b] One study only [11]; two studies using high-titer measles vaccine not included [23, 30].

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