Paediatric HIV testing beyond the context of prevention of mother-to-child transmission: a systematic review and meta-analysis

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Summary

Background Many HIV-positive children in low-income and middle-income countries remain undiagnosed. Although HIV testing in children at health facilities is recommended by WHO, it is not well implemented. This systematic review and meta-analysis examines the case-finding benefit of HIV screening in children aged 0–5 years in low-income and middle-income countries.

Methods We did this systematic review and meta-analysis in accordance with an a-priori protocol. We searched PubMed, MEDLINE, WHO Global Index Medicus, Web of Science, Médecins Sans Frontières, Cochrane, Embase, CABS Abstracts, and LILACS databases for articles published between Jan 1, 2004, and April 30, 2016, that reported the quantitative prevalence of HIV detected through screening in four key contexts (paediatric inpatient settings, paediatric outpatient settings, nutrition centres, and expanded programme on immunisation centres) in paediatric populations in low-income and middle-income countries. Articles were identified and data were extracted in duplicate. The primary outcome was HIV prevalence, for which we used a DerSimonian-Laird random-effects meta-analysis to pool prevalence data and 95% CIs. We did stratified analyses according to geographical context and testing strategy. This study is registered with PROSPERO, number CRD42014014372.

Findings Our search found 2996 studies, of which 26 met the inclusion criteria. Paediatric HIV prevalence across all settings was 15·6% (95% CI 11·8–19·5). HIV prevalence by setting was highest in paediatric inpatient settings (21·1%, 95% CI 14·9–27·3), followed by nutrition centres (13·1%, 95% CI 3·4–22·7), expanded programme on immunisation centres (3·3%, 95% CI 0–6·9), and paediatric outpatient settings (2·7%, 95% CI 0·3–5·2). Universal testing and testing triggered by symptoms had similar diagnostic yield in the inpatient setting (21·3%, 95% CI 11·6–31·0 in triggered testing *vs* 20·9%, 95% CI 13·5–28·3 in universal testing).

Interpretation HIV testing in paediatric populations in low-income and middle-income countries outside the context of prevention of mother-to-child transmission programmes provides an important opportunity to identify HIV-positive children. For countries wishing to prioritise interventions, the highest diagnostic yields were obtained from inpatient wards and nutrition centres. Universal testing might be the preferred approach since it did not have a substantially lower diagnostic yield than triggered testing

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Introduction

Despite the substantial gains made from scale-up of programmes targeting the prevention of mother-to-child transmission (PMTCT) of HIV, 240 000 children are estimated to be newly infected each year.[1] With 3·2 million children living with HIV, but only 740 000 on antiretroviral therapy (ART), paediatric HIV care and treatment lags behind that of adults and a substantial number of children remain undiagnosed.[1] One estimate from Kenya suggests that only 40% of children with HIV are diagnosed.[2] This number is likely to be even lower for countries with the weakest health systems and lowest HIV programme coverage. Although PMTCT coverage and efficacy of preventing transmission to infants is improving, many gaps remain in the PMTCT system, including mother and child pairs who are lost to follow-up and HIV-infected pregnant or breastfeeding women who never enter the PMTCT system. In 2014, among the 21 UNAIDS priority countries, 77% of HIV-infected pregnant women received ART. However, this number belies large differences between countries, with some having coverage less than 30%, and less than 50% of infants receiving an appropriate diagnostic test by 2 months of age in the priority countries.[1]

Improvements in programmes are essential to identify children living with HIV and to link them to care and ART initiation. Improved paediatric HIV case finding will also be necessary to meet the UNAIDS 90–90–90 goals. Existing WHO guidance recommends that, in generalised epidemics, provider-initiated testing and counselling (PITC) should be offered to all adults, adolescents, and children who present to health facilities.[3] In concentrated and low-prevalence contexts, PITC is recommended in all health facilities, but restricted to HIV-exposed children or those presenting with symptoms suggestive of HIV infection.

Research in context

Evidence before this study

Although WHO recommends provider-initiated testing and counselling for paediatric populations in all health-care contexts with generalised HIV epidemics, this recommendation is very poorly implemented, resulting in missed opportunities to diagnose and treat children living with HIV. Although many studies have described the prevalence of paediatric HIV detected by testing in various health-care settings, there has not been a systematic review of this literature to describe the body of evidence, and to assess the overall consistency and quality of the evidence. Nor has there been a meta-analysis to compare the diagnostic yield of testing in different types of health-care facilities or different testing strategies. Before starting this study, we discussed the question of identifying contexts where HIV screening in paediatric populations would result in highest yield with the WHO treatment and care team and searched PubMed and Embase to April 30, 2014, with broad search terms (HIV, paediatric search terms, testing search terms, and terms to identify low-income and middle-income countries) for any other existing reviews of this evidence. Because our search did not identify a pre-existing review and the WHO team identified this as an important question to inform the 2015 Consolidated HIV Treatment Guidelines, a full systematic review was initiated.

Added value of this study

To our knowledge, this systematic review and meta-analysis is the first to examine the diagnostic yield of HIV testing in paediatric populations in four key health care contexts: paediatric inpatient settings, nutrition centres, immunisation clinics, and paediatric outpatient clinics. The review also compares the diagnostic yield among these contexts to help provide information for programmatic priorities and planning. The review describes several secondary outcomes, such as caregiver acceptance rates, that could also be used to inform the development of paediatric HIV testing programmes.

Implications of all the available evidence

Our results show very high prevalence of paediatric HIV in the under-five population in some health-care settings, particularly paediatric inpatient and nutrition centres. Furthermore, universal screening resulted in a nearly equal diagnostic yield compared with screening that was triggered by a specific symptom. In view of the UNAIDS 90–90–90 goals and the fact that a substantial number of children remain undiagnosed, the findings of this study are important for countries and other implementers attempting to prioritise interventions to diagnose paediatric HIV and link patients to care. Universal screening of all paediatric patients presenting to inpatient or nutrition centres has a very high diagnostic yield and likely represents an important opportunity to link patients to care and treatment. Programmes should prioritise interventions to strengthen testing in these settings. Further operational research on how to ensure patients identified in these settings are linked to care and receive antiretroviral therapy is needed.

However, PITC for paediatric populations outside the setting of PMTCT is not being optimally implemented.[4] Reasons cited for the poor uptake of WHO-recommended PITC include misperceptions about the importance of HIV testing in children after infancy and insufficient resources and time, and legal frameworks that make testing children difficult without legal guardian consent.[5] To improve implementation of PITC outside the context of PMTCT, it will be necessary to direct programmes towards improving education and awareness of health-care workers about the importance of paediatric HIV testing, increase resources in key contexts, and address legal barriers. National programmes and other implementers will need evidence on which facilities can provide the highest screening efficiency or yield and which testing programme strategies result in the lowest number needed to test to identify an HIV-positive child.

We did this systematic review to provide additional evidence about PITC for paediatric populations outside the PMTCT context and to investigate whether any particular contexts or testing strategies should be prioritised for PITC. Specifically, the review addressed the question, for children aged 0–5 years in low-income and middle-income countries, does HIV screening in four key contexts (paediatric inpatient settings, paediatric outpatient settings, nutrition centres, and expanded programme on immunisation [EPI] centres) enable an improved yield of HIV diagnosis compared with screening in PMTCT settings, and if so, which provide the highest yield for HIV testing?

For the **protocol** see http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014014372

Methods

Search strategy and selection criteria

Before starting this systematic review and meta-analysis, we prepared a protocol for the literature search, article selection, data extraction, and assessment of methodological quality, which is available online. Randomised controlled trials, case-control, cohort, and cross-sectional study designs were eligible for inclusion. We excluded studies published before 2004 when appropriate nucleic acid testing was very uncommon in low-income and middle-income countries and coverage of PMTCT was low; data published since are more relevant to the current situation.

We selected articles that provided quantitative HIV prevalence data resulting from the provision of HIV screening tests to paediatric populations outside PMTCT contexts. We excluded studies that reported on paediatric HIV prevalence resulting from testing for diagnostic, rather than screening purposes, such as studies in which PCR for HIV was done after a positive rapid HIV diagnostic

test. Additionally, studies that were set in tuberculosis clinics or tuberculosis inpatient wards were excluded because the critical importance and high diagnostic yield in children with tuberculosis infection is well.

We included studies of paediatric populations if patients were aged 0–12 years, had unknown HIV status or a previous negative test, and were from paediatric inpatient settings, paediatric outpatient settings, nutrition centres, or EPI centres in countries designated as low-income or middle-income countries at the time of the study. We then selected a subset of studies that included data from patients aged 0–5 years for our study. For studies including patients older than 5 years, we included the data in this analysis if the manuscript contained age-disaggregated data or the authors responded to requests for age-disaggregated data.

We searched PubMed, MEDLINE, WHO Global Index Medicus, Web of Science, Médecins Sans Frontières, Cochrane, Embase, CABS Abstracts, and LILACS databases for French and English language manuscripts published between January, 2004, and April, 2016, with the relevant search terms (appendix pp 1–7). We did the search between September and November, 2014, with an updated search in April, 2016, to identify additional manuscripts published after November, 2014.

The title, abstract, and full-text were reviewed in duplicate by JT and KL, with a third reviewer (JC) serving as a tie-breaker for inclusion disagreements. The reference lists for articles selected for inclusion were also assessed to identify additional manuscripts to review. Additional data and clarifications were sought by contacting study authors.

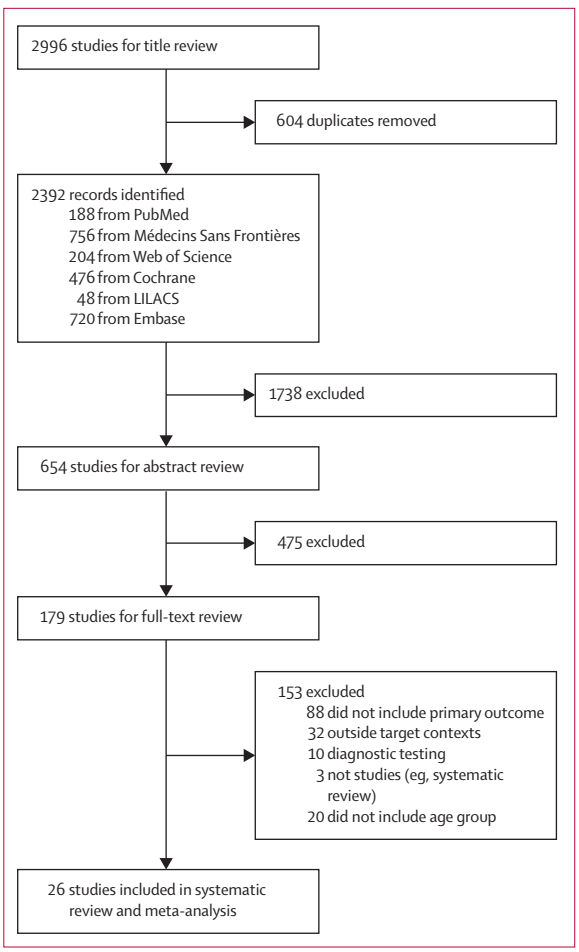

Figure 1: **Study selection**

See Online for appendix

Data analysis

The primary outcome measure was paediatric HIV prevalence (ie, the number of HIV-positive children among those tested in a given context). Secondary outcomes were caregiver acceptance of HIV testing, health-care worker uptake of HIV testing recommendations or protocols, and subsequent retention in care, including linkage to care and ART initiation.

Data were extracted in duplicate on to a predefined data extraction form. We extracted information about the type of study (study design), setting (country, health setting), screening approach (triggered or universal testing), screening tests used, the primary outcome of HIV prevalence by age (disaggregated where possible for children aged 5 years and younger and aged 5–12 years), and secondary outcomes (caregiver acceptance of paediatric HIV testing, health provider uptake of paediatric HIV testing, and retention at sequential steps in the care cascade to antiretroviral initiation). We compared details of the populations described, location, and authors to ensure duplicate data from the same cohort were not reported. We used the modified Newcastle-Ottawa scale for cross-sectional studies to assess quality (appendix pp 8, 9).

For the primary outcome of paediatric HIV prevalence, we used a DerSimonian-Laird random-effects meta-analysis to pool prevalence values and 95% CIs. We assessed between-study heterogeneity with the I^2 statistic. We did stratified analysis by geographical location and mode of HIV screening (universal screening *vs* triggered symptom-based screening). We used the Mann-Whitney *U* test for comparisons between groups. For the secondary outcome of caregiver acceptance rates, we used descriptive statistics. We used OpenMetaAnalyst for all statistical analyses

This study is registered with PROSPERO, number CRD42014014372.

Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Our search yielded 2996 unique studies for consideration, of which 26[6–31] met the criteria for inclusion in the review

(figure 1) and included data on children younger than 5 years (table). Most studies contained data on children aged 0–6·0 months and, where available, the age strata are presented. One study provided data for both EPI centres and paediatric outpatient settings; in the analysis, these different contexts were analysed separately.[20] Data from 33 549 children were included. Geographically, most studies were located in sub-Saharan Africa (24 studies),[8–31] with one study each in Asia[6] and Oceania.[7] Paediatric inpatient programmes were the most common context (17),[6,7,10,13–19,21–25,29,30] followed by nutrition centres (four),[9,11,12,27] EPI centres (three),[20,26,28] and paediatric outpatient

	Country	Context	Study design	Testing approach	Tests used	HIV prevalence	HIV prevalence by age	Caregiver acceptance
Ali et al, 2007[6]	India	Inpatient	Cross-sectional	Triggered	Serology (ELISA)	0/300 (0%)	0–17 months: 0/140 18–35 months: 0/66 36–60 months: 0/94	300/300 (100%)
Allison et al, 2011[7]	Papua New Guinea	Inpatient	Cross-sectional	Universal	Serology	55/487 (11·3%)	NA	NA
Arscott-Mills et al, 2014[8]	Botswana	Outpatient	Cross-sectional	Triggered	Serology (ELISA); PCR for children aged <18 months	0/45 (0%)	NA	NA
Asafo-Agyei et al, 2013[9]	Ghana	Nutrition centre	Cross-sectional	Universal	Two rapid HIV antibody tests: First Response and Oraquick; confirmatory ELISA for discordant results	62/240 (25·8%)	3–18 months: 37/140 (21·4%) 18–60 months, 25/100 (24%)	246/246 (100%)
Bachou et al, 2006[10]	Uganda	Inpatient	Cross-sectional	Triggered	Serology (ELISA); PCR for children aged <18 months	123/315 (39·1%)	0–5·9 months: 3/11 (27·3%) 6–11·9 months: 23/58 (39·7%) 12–23·9 months: 57/160 (35·6%) 24–35·9 months: 25/50 (50%) 36–47·9 months: 8/20 (40%) 48–59·9 months: 7/16 (43·7%)	NA
Bahwere et al, 2008[11]	Malawi	Nutrition centre	Cross-sectional	Universal	Two rapid tests (Determine and Unigold); PCR for children aged <18 months	45/1523 (3%)	0–12 months: 9/219 (4·1%) 12–60 months: 36/1304 (2·8%)	1174/1273 (92%)
Chinkhumba et al, 2008[12]	Malawi	Nutrition centre	Cross-sectional	Universal	Two rapid tests (Determine and Unigold); Western blot for discordant; PCR for children aged <18 months	79/545 (14·5%)	NA	506/621 (81%)
Cohen et al, 2013[13]	South Africa	Inpatient	Cross-sectional	Triggered	Serology (ELISA); PCR for children aged <18 months	238/368 (64·7%)	NA	NA
Creek et al, 2010[14]	Botswana	Inpatient	Cross-sectional	Triggered	Two rapid tests (Determine and Unigold); PCR for children aged <18 months	23/131 (17·6%)	NA	NA
De Maayer et al, 2011[15]	South Africa	Inpatient	Cross-sectional	Triggered	Serology (ELISA); PCR for children aged <18 months	31/82 (37·8%)	NA	NA
Hallbauer et al, 2014[17]	South Africa	Inpatient	Cross-sectional	Triggered	Serology (ELISA); PCR for children aged <18 months	2/20 (10%)	0–24 months: 2/3 (67%) 24–60 months: 0/17 (0%)	NA
Huang et al, 2013[16]	Malawi	Inpatient	Cross-sectional	Universal	Two rapid tests	8/55 (14·5%)	18 months to 4·9 years (no further breakdown)	NA (73%)
Kankasa et al, 2009[18]	Zambia	Inpatient	Cross-sectional	Universal	Two rapid tests (Determine and Genie II); PCR for children aged <18 months	3100/10466 (29·6%)	0–12 months: 1849/5942 (31·1%) 12–18 months: 500/1620 (30·9%) 18–60 months: 751/2904 (25·9%)	11571/13239 (87%)
McCollum et al, 2012[20] (EPI)	Malawi	EPI	Cross-sectional	Universal	Rapid test; PCR for children aged <18 months	6/880 (0·7%)	NA	70/70 (100%)
McCollum et al, 2012[20] (outpatient)	Malawi	Outpatient	Cross-sectional	Universal	Rapid test; PCR for children aged <18 months	43/874 (4·9%)	NA	28/31 (90%)
McCollum et al, 2010[19]	Malawi	Inpatient	Cross-sectional	Universal	Rapid test; PCR for children aged <18 months	527/5531 (9·5%)	8 to 50 months (no further breakdown)	5531/5657 (98%)
Nansera et al, 2012[21]	Uganda	Inpatient	Cross-sectional	Triggered	Two rapid tests (Determine and Chembio); Confirmatory Unigold for discordant; PCR for children aged <18 months	78/468 (16·6%)	0 to 24 months (no further breakdown)	NA
Nathoo et al, 2012[22]	Zimbabwe	Inpatient	Cross-sectional	Universal	Serology (ELISA); PCR for children aged <18 months	203/355 (57·1%)	2–18 months (no further breakdown)	355/363 (98%)
Obiagwu et al, 2013[23]	Nigeria	Inpatient	Cross-sectional	Universal	Rapid test (Determine); PCR for children aged <18 months	18/142 (12·7%)	0–12 months: 8/58 (13·8%) 12–24 months: 4/38 (10·5%) 24–36 months: 3/32 (9·4%) 36–48 months: 2/9 (22·2%) 48–60 months: 1/5 (20·0%)	NA

(Table continues on next page)

	Country	Context	Study design	Testing approach	Tests used	HIV prevalence	HIV prevalence by age	Caregiver acceptance
(Continued from previous page)								
Pavlinac et al, 2015[24]	Kenya	Inpatient	Cross-sectional	Triggered	Rapid test (Determine); PCR for children aged <18 months	3/148 (2·0%)	6 to 60 months (no further breakdown)	NA
Rogerson et al, 2004[25]	Malawi	Inpatient	Cross-sectional	Universal	Rapid test (Determine); PCR for children aged <18 months	161*/820 (19·6%)	0–6 months: 53/166 (31·9%) 6–15 months: 38/248 (15·3%) 15–35 months: 56/291 (19·2%) 35–59 months: 15/115 (13·0%)	NA
Rollins et al, 2009[26]	South Africa	EPI	Cross-sectional	Universal	Serology (Vironostika); PCR for children aged <18 months	54/584 (9·2%)	6 weeks to 18 months (no further breakdown)	584/646 (90%)
Rytter et al, 2015[27]	Uganda	Nutrition centre	Cross-sectional	Universal	Serology; PCR for children aged <18 months	9/93 (9·7%)	5–59 months (no further breakdown)	NA
Udo et al, 2013[28]	Nigeria	EPI	Cross-sectional	Universal	Two rapid tests (Determine and Chembio); PCR for children aged <18 months	1/147 (0·7%)	0–9 months (no further breakdown)	NA
Wanyenze et al, 2010[29]	Uganda	Inpatient	Cross-sectional	Universal	Two rapid tests (Determine and Chembio); Confirmatory Unigold for discordant; PCR for children aged <18 months	991/7625 (13%)	0–12 months: 443/2888 (15·3%) 12–60 months: 548/4737 (11·6%)	8990/9687 (93%)
Webb et al, 2012[30]	Kenya	Inpatient	Cross-sectional	Triggered	Rapid test	30/568 (5·3%)	NA	NA
Zoufaly et al, 2014[31]	Cameroon	Outpatient	Cross-sectional	Universal	Two rapid tests (Determine and Hexagon); PCR for children aged <18 months	13/737 (1·8%)	0–18 months: 6/507 (1·2%) 18–60 months: 7/230 (3·0%)	981/1010 (97%)

Manufacturers of diagnostic tests are as follows: Determine, Alere, Matsudo, Japan; First Response, Premier Medical Corporation, Daman, India; OraQuick, OraSure Technologies, Bethlehem, PA USA; Unigold, Trinity Biotech, Bray, Ireland; Genie II, Bio-Rad, Marnes-la-Coquette, France; Chembio, Medford, NY, USA; Vironostika, Organon Teknika, Durham, NC, USA; and Hexagon, HUMAN Gesellschaft fur Biochemisch und Diagnostica, Wiesbaden, Germany. NA=not applicable. EPI=expanded programme on immunisation. *Discrepancy with age breakdown in original study.

Table: **Study-level characteristics of included manuscripts**

programmes (three).[8,20,31] The assessment for quality showed that most of the included studies (20)[9–12,15–20,22–31] were of fair or good quality and the remainder (six)[6–8,13,14,21] were of poor quality (appendix pp 8–9).

Across all settings, overall paediatric HIV prevalence was 15·6% (95% CI 11·8–19·5; figure 2). By setting, prevalence was highest in paediatric inpatient settings (21·1%, 95% CI 14·9–27·3), followed by nutrition centres (13·1%, 95% CI 3·4–22·7), EPI centres (3·3%, 95% CI 0–6·9), and outpatient settings (2·7%, 95% CI 0·3–5·2; figure 3). No study contained a direct comparison of HIV prevalence in any of the four study settings with that in PMTCT settings, so direct comparison was not possible.

We did a stratified analysis of paediatric HIV prevalence in southern and eastern Africa (20 studies)[8,10–22,24–27,28,29] versus that in west and central Africa (four).[9,23,28,31] Paediatric HIV prevalence across contexts in southern and eastern Africa was 17·8% (95% CI 12·8–22·7) and prevalence in west and central Africa was 9·8% (95% CI 4·2–15·3). Because of the small numbers of studies from Asia and Oceania, these geographical settings were not included in stratified analyses. We did stratified analysis examining universal (eight studies)[7,16,18,19,22,23,25,29] versus triggered testing (nine)[6,10,13–16,22,24,30] in inpatient settings. Paediatric HIV prevalence detected via triggered testing (21·3%, CI 11·6–31·0) was slightly, but not significantly (p=0·95), higher than that detected with universal testing (21·2%, 13·8–28·7; appendix pp 10–11).

12 studies reported caregiver acceptance of HIV testing.[6,9,11,12,16,18–20,22,26,29,31] 11 of these studies were from sub-Saharan Africa[9,11,12,16,18–20,22,26,29,31] and one was from India.[6] These studies examined inpatient settings (six),[6,16,18,19,22,29] nutrition centres (three),[9,11,13] EPI centres (two),[20,26] and outpatient settings (two),[20,31] with one study examining both outpatient and EPI centres.[20] The unweighted mean for caregiver acceptance across twelve studies (13 settings) was 92·2% (range 73–100). Several studies described the reasons for caregiver uptake or refusal of HIV testing.[11,16,18] Caregivers were motivated by wanting to know the status of their children and by concern that their children were often ill. Reasons for refusal included fear of a positive result, not feeling ready to know the child's status and (in the case of female caregivers) the need to discuss with the caregiver's husband.

No quantitative data were identified for the secondary outcome of health-care worker uptake. Two studies[18,20] reported qualitatively on health-care worker uptake of HIV. One study[18] noted that repeated sensitisation workshops were necessary to maintain health-care worker uptake of PITC. Reasons identified for health-care workers not offering HIV testing included perceptions that the child was too young or too sick for testing or that a heavy workload precluded them from being able to provide testing.[18] The second study[20] noted that health-care workers in inpatient departments were seven times more likely to offer HIV testing than were those in under-five outpatient clinics.

Three studies reported on retention in care, all of which were from sub-Saharan Africa.[19,20,26] These studies examined three contexts: inpatient (one study),[18] EPI (two),[20,26] and outpatient (one).[20] The proportion of caregivers who returned for test results was reported to

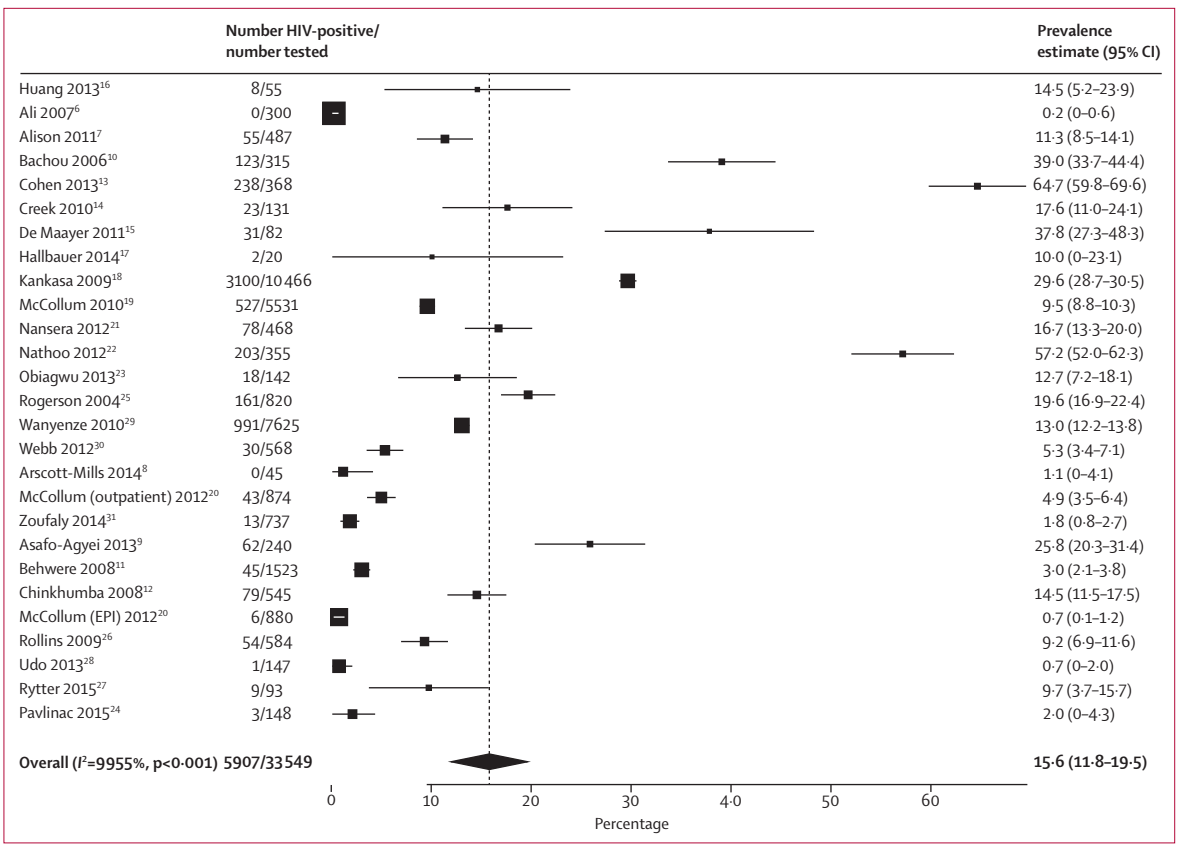

Figure 2: **Overall paediatric HIV prevalence**
EPI=Expanded programme on immunisation.

be 25% in the outpatient setting, 56·8% in EPI centres, [26] and 78·6% in the inpatient centres.[20] One study[19] reported that 68·3% of patients were successfully enrolled into HIV care following HIV testing in an inpatient setting.

We detected high heterogeneity overall (99·55%) and for each of the contexts (99·50% in inpatient settings, 98·15% in outpatient settings, 98·02% in nutrition centres, and 94·17% in EPI centres). This heterogeneity remained when we only studied a single context in a given region and when we looked at studies by recent and more distant date ranges and study quality according to the Newcastle-Ottawa tool (appendix pp 8, 9). However, because we had insufficient background information about potential covariates such as paediatric HIV prevalence in each country in patients younger than 5 years, local HIV prevalence in pregnant women, PMTCT programme coverage, the PMTCT regimen used, and retention in the early infant diagnosis cascade, we did not do a meta-regression.

Discussion

Our results show that HIV testing in paediatric populations in key health-care contexts outside PMTCT programmes in low-income and middle-income countries provides an important opportunity to identify HIV-positive children. The overall paediatric HIV prevalence of 15·6% in all studies and contexts, as well as the prevalence in paediatric inpatient settings (21·1%) and nutrition centres (13·1%), represent a high yield for HIV testing. These findings might be related to the fact that children presenting to inpatient and nutrition centres are symptomatic and thus have a higher pretest probability of being HIV positive than do healthy children presenting to EPI and outpatient settings. Since most children included in this review had previously unknown HIV status, including some with unknown HIV exposure status, these children might have been less likely to have benefitted from PMTCT than children with known status, which might explain the relatively high prevalence of HIV in these settings.

The studies included in this systematic review suggest that, within the four contexts assessed, use of paediatric HIV testing in inpatient and nutrition centres would give the highest yield of HIV-positive individuals. Furthermore, when examining the most commonly assessed context, paediatric inpatient facilities, both triggered and universal testing yielded high paediatric HIV prevalence. Although triggered testing identified a slightly larger proportion of HIV-positive people out of those tested, this was not significantly different to the proportion

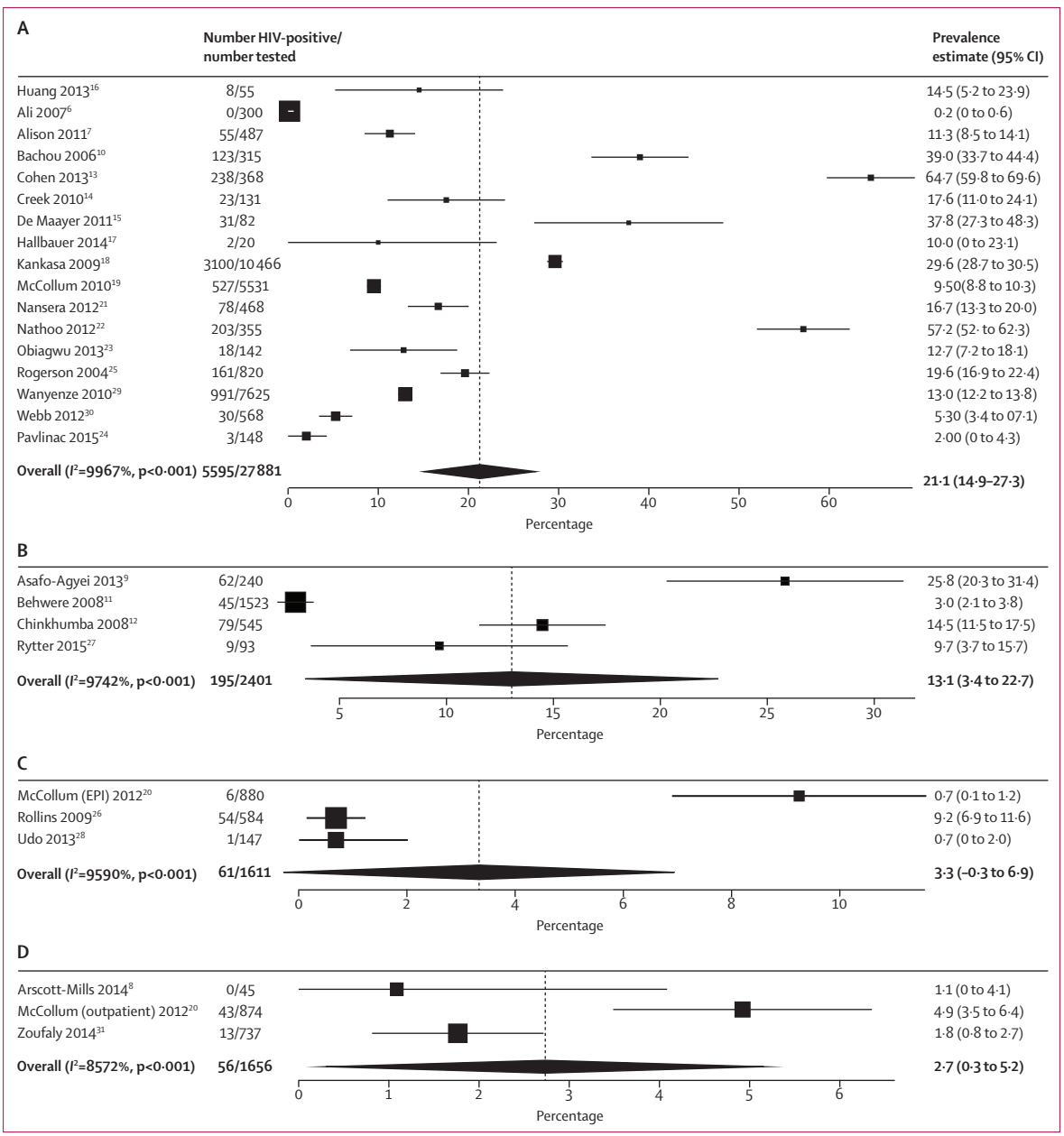

Figure 3: Paediatric HIV prevalence in four contexts
HIV prevalence is shown for inpatient settings (A), nutrition centres (B), EPI centres (C), and paediatric outpatient settings (D). EPI=expanded programme on immunisation.

detected with universal testing. Given that both proportions are very high, universal testing seems like a reasonable option in the context of paediatric inpatient programmes. This finding has important programmatic implications; a universal testing strategy might reduce barriers to the provision of HIV testing for children and might simplify training for health workers. We could not do a similar comparison in the other contexts because of the small numbers of studies and use of universal testing in nearly all studies examining nutrition, EPI or outpatient contexts.

Testing outside the PMTCT context might be of particular relevance to areas with low PMTCT coverage, such as many countries in central and west Africa. In view of the lower general adult HIV prevalence in west and central Africa lower than in east and southern Africa (1·5–4·8% for countries included in our review), the average paediatric HIV prevalence of 9·8% was relatively high.[32] In the single study that examined testing in a nutrition centre in Ghana, paediatric HIV prevalence detected with universal testing was 22%.

Our analysis of secondary outcomes provides valuable

insight into the feasibility of scaling up paediatric HIV testing outside PMTCT contexts. Caregiver acceptance was very high, suggesting that caregivers are motivated by their child's illness to find an underlying cause, especially in inpatient or nutrition settings. To address caretaker-identified barriers, such as fear of a positive result or the need for the husband's approval, education and counselling to explain the benefits of diagnosis and treatment should be available.

We found substantially less information about health-care worker uptake in the selected articles. The small amount of data that we had showed that health-care worker uptake of paediatric HIV testing will need to be supported through additional resources and repeated sensitisations. Furthermore, the extent of health-care worker uptake might be context dependent. Competing demands on health-care workers in busy settings (eg, outpatient clinics or EPI sites) might limit the inclusion of HIV testing in the workflow compared with settings in which patients might spend longer periods of time (eg, inpatient paediatric sites or nutrition centres). A goal of future operational research should be to define and optimise a support and resource package to help health-care workers to implement HIV testing in high-yield, non-PMTCT contexts.

Information about the linkage of children identified as HIV-positive to care and subsequent treatment was also scarce and further research is needed. Worryingly, the evidence available suggested very little provision of test results to caregivers and low levels of linkage to care. Given that we noted high loss to follow-up at the results management stage, early in the care pathway, it is crucial that point-of-care testing, including nucleic acid testing for children younger than 18 months, be made available in low-income and middle-income countries. Although provision of rapid serological tests is feasible with minimum training and laboratory infrastructure, the same might not be true of point-of-care nucleic acid testing and further studies needed to better define the feasibility of providing such tests at sites such as nutrition treatment centres. Furthermore, the process of referring HIV-positive children to care might not be well defined and might be difficult to navigate for health-care workers and parents alike. In the implementation and strengthening of paediatric HIV testing in non-PMTCT contexts, the process of linkage to care needs to be better defined and support given to parents to ensure that the family is able to follow up on the test results in an HIV clinic.

This systematic review has several limitations. First, most studies identified were from sub-Saharan Africa and thus our conclusions might not be generalisable to other geographical contexts. Only a few studies were included that described HIV testing in the context of EPI centres, outpatient settings, and nutrition centres. Additional research in geographical areas outside sub-Saharan Africa and in nutrition, EPI, and outpatient settings is needed to inform appropriate approaches in these contexts. Second, this review was restricted to articles published from 2004 onward. Subsequent improvements in PMTCT and ART enrolment have occurred more recently, which might affect the yield of HIV testing outside PMTCT settings. However, most studies included in this review were published after 2010 and there did not seem to be a systematic temporal trend in paediatric HIV prevalence. Finally, the review was not designed to select systematically for studies that contained secondary outcomes, but did not contain the primary outcome. Thus, the small body of evidence on secondary outcomes in this review might not be representative of the broader landscape of the acceptability and uptake of HIV testing, or the retention of HIV positive patients in the care cascade.

To meet the UNAIDS 90-90-90 goals, improved case finding is needed. As coverage of PMTCT improves, infants tested in this context will be more likely to remain HIV-negative those in mother–infant pairs that did not access PMTCT services. However, to reach the UNAIDS goals and to improve the health of children living with HIV, these missed cases will need to be found. Although WHO recommends PITC in children, this approach is poorly implemented. Our systematic review provides evidence for high-yield HIV screening of children in inpatient sites and nutrition clinics, and provides data for countries and other programme implementers that might want to focus limited resources on universal HIV testing. Financial and human resource investments will be needed to integrate universal HIV testing into these sites and further operational research will help to define packages of training for health workers and ensure linkage to care for HIV-positive patients. Additional barriers, such as legal restrictions, caretaker consent, or inadequate laboratory infrastructure to support point-of-care nucleic acid testing will also need to be addressed. Very high levels of parental acceptance suggest that this intervention is desired by families who wish to provide the best care for their children and that parental refusal will not be a substantial barrier. Universal HIV testing in high-yield, non-PMTCT contexts will contribute to a reduction of preventable paediatric HIV deaths, bringing the 90-90-90 goals one step closer.

Contributors

JC and KW developed the protocol, assisted with the literature search and data extraction, analysed and interpreted the data, and wrote the manuscript. JT and KL did the literature search and data extraction. TT assisted with analysis. All authors contributed to editing the manuscript.

Declaration of interests

We declare no competing interests.

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