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Point-of-care tests detecting HIV nucleic acids for diagnosis of HIV-1 or HIV-2 infection in infants and children aged 18 months or less (Review)

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[Diagnostic Test Accuracy Review]

Point-of-care tests detecting HIV nucleic acids for diagnosis of HIV-1 or HIV-2 infection in infants and children aged 18 months or less

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ABSTRACT

Background

The standard method of diagnosing HIV in infants and children less than 18 months is with a nucleic acid amplification test reverse transcriptase polymerase chain reaction test (NAT RT-PCR) detecting viral ribonucleic acid (RNA). Laboratory testing using the RT-PCR platform for HIV infection is limited by poor access, logistical support, and delays in relaying test results and initiating therapy in low-resource settings. The use of rapid diagnostic tests at or near the point-of-care (POC) can increase access to early diagnosis of HIV infection in infants and children less than 18 months of age and timely initiation of antiretroviral therapy (ART).

Objectives

To summarize the diagnostic accuracy of point-of-care nucleic acid-based testing (POC NAT) to detect HIV-1/HIV-2 infection in infants and children aged 18 months or less exposed to HIV infection.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (until 2 February 2021), MEDLINE and Embase (until 1 February 2021), and LILACS and Web of Science (until 2 February 2021) with no language or publication status restriction. We also searched conference websites and clinical trial registries, tracked reference lists of included studies and relevant systematic reviews, and consulted experts for potentially eligible studies.

Selection criteria

We defined POC tests as rapid diagnostic tests conducted at or near the patient site. We included any primary study that compared the results of a POC NAT to a reference standard of laboratory NAT RT-PCR or total nucleic acid testing to detect the presence or absence of HIV infection denoted by HIV viral nucleic acids in infants and children aged 18 months or less who were exposed to HIV-1/HIV-2 infection. We included cross-sectional, prospective, and retrospective study designs and those that provided sufficient data to create the 2 × 2 table to calculate sensitivity and specificity. We excluded diagnostic case control studies with healthy controls.

Data collection and analysis

We extracted information on study characteristics using a pretested standardized data extraction form. We used the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool to assess the risk of bias and applicability concerns of the included studies. Two review authors independently selected and assessed the included studies, resolving any disagreements by consensus. The unit of analysis was the participant. We first conducted preliminary exploratory analyses by plotting estimates of sensitivity and specificity from each study on forest plots and in receiver operating characteristic (ROC) space. For the overall meta-analyses, we pooled estimates of sensitivity and specificity using the bivariate meta-analysis model at a common threshold (presence or absence of infection).

Main results

We identified a total of 12 studies (15 evaluations, 15,120 participants). All studies were conducted in sub-Saharan Africa. The ages of included infants and children in the evaluations were as follows: at birth (n = 6), ≤ 12 months (n = 3), ≤ 18 months (n = 5), and ≤ 24 months (n = 1). Ten evaluations were field evaluations of the POC NAT test at the point of care, and five were laboratory evaluations of the POC NAT tests.The POC NAT tests evaluated included Alere q HIV-1/2 Detect qualitative test (recently renamed m-PIMA q HIV-1/2 Detect qualitative test) (n = 6), Xpert HIV-1 qualitative test (n = 6), and SAMBA HIV-1 qualitative test (n = 3).

POC NAT pooled sensitivity and specificity (95% confidence interval (CI)) against laboratory reference standard tests were 98.6% (96.1 to 99.5) (15 evaluations, 1728 participants) and 99.9% (99.7 to 99.9) (15 evaluations, 13,392 participants) in infants and children ≤ 18 months.

Risk of bias in the included studies was mostly low or unclear due to poor reporting. Five evaluations had some concerns for applicability for the index test, as they were POC tests evaluated in a laboratory setting, but there was no difference detected between settings in sensitivity (−1.3% (95% CI −4.1 to 1.5)); and specificity results were similar.

Authors' conclusions

For the diagnosis of HIV-1/HIV-2 infection, we found the sensitivity and specificity of POC NAT tests to be high in infants and children aged 18 months or less who were exposed to HIV infection.

PLAIN LANGUAGE SUMMARY

Point-of-care tests for detecting HIV viral molecules in infants and children aged 18 months or less

Why is improving the diagnosis of HIV infection important?

It is estimated that 1.5 million infants are still exposed to HIV every year. If left untreated, about 50% to 60% of HIV-infected infants will die by the age of two years. Children infected before birth are especially at high risk of death. HIV is incurable; however, there are medications that suppress HIV, known as antiretroviral drugs (ART). When HIV is detected early, severe illness and death from HIV-related infections can be prevented by taking this medication. A test that detects HIV viral genetic molecules quickly and accurately at or near the patient's side (point-of-care) therefore can increase access to early appropriate treatment and minimize missing treatments in those whose HIV remains undetected.

What is the aim of this review?

To determine the accuracy of molecular point-of-care tests for detecting the main types of HIV infection (HIV-1/HIV-2) in infants and children aged 18 months or less.

What was studied in this review?

Published reports of molecular point-of-care tests with results measured against laboratory viral-based tests (benchmark).

What are the main results of this review?

Twelve studies which completed 15 evaluations involving 15,120 participants compared molecular point-of-care tests for diagnosing HIV infection.

What are the strengths and limitations of this review?

The review included sufficient studies and participants. All studies were conducted in sub-Saharan Africa, making the results highly applicable for use in communities where the disease is regularly found and where disease control programmes are often targeted. However, one in three included evaluations of the molecular point-of-care tests were conducted in a laboratory setting and not near the patient but there was no difference in the test accuracy between settings.

To whom do the results of this review apply?

Infants and children aged 18 months or less who were exposed to HIV infection.

What are the implications of this review?

In theory, for a population of 1000 children aged 18 months or less where 100 have HIV infection, 100 children will be positive with the molecular point-of-care test, of which one will not have the infection (false-positive result), and 900 will be negative with the molecular point-of-care test, of which one will indeed have the infection (false-negative result).

How up-to-date is this review?

The evidence is current to 2 February 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Point-of-care nucleic acid-based testing for HIV infection in infants and children aged ≤ 18 months

Review question: What is the diagnostic accuracy of point-of-care nucleic acid-based testing for the detection of HIV infection in HIV-exposed infants and children aged ≤ 18 months?	
Population	HIV-exposed infants and children aged ≤ 18 months
Index test	Point-of-care nucleic acid-based testing (POC NAT). Test types: Xpert HIV-1 (n = 6), SAMBA HIV-1 (n = 3), and Alere HIV-1/2 (renamed m-PIMA) (n = 6)
Threshold for index test	Results presented qualitatively as presence or absence of viral ribonucleic acid (RNA)
Reference standard	Laboratory-based virological l assays to detect viral nucleic acid
Settings	Primary care settings or local hospitals
Studies	Cross-sectional studies
Action	If accurate, index test results will decide on initiation of drug therapy, and replace the reference standard of laboratory testing.

Limitations	**TEST: POC NAT THRESHOLD: dichotomous data (Yes/No)**
Risk of bias	**Some concerns about risk of bias**
	1 study had a high risk of bias for participant selection, but risk of bias was mostly low for the included studies.
Applicability of evidence to question	**Some concerns about applicability for the index test**
	1 in 3 evaluations of the POC NAT test was done in a laboratory setting rather than at or near patient care.
	All evaluations were conducted in sub-Saharan Africa, making the results highly applicable for use in endemic communities where disease control programmes are often targeted.

Findings	**TEST: POC NAT THRESHOLD: dichotomous data (Yes/No)**

	Quantity of evidence	12 studies (15 evaluations)	**Total participants**	15,120	**Total with target condition**	1728
Accuracy	Consistency: minimal heterogeneity between estimates of sensitivity and specificity					
Effect (95% CI)[a]	**Test result**		**Number of results per 1000 patients tested (95% CI)**			**Number of participants**
			Prevalence 2.5%[b]	**Prevalence 10%**[b]	**Prevalence 30%**[b]	
Pooled sensitivity 98.6% (96.1 to 99.5)	**True-positives**	Will receive appropriate drug treatment	25 (24 to 25)	99 (96 to 100)	296 (288 to 299)	1728
	False-negatives	Will not receive required drug treatment	0 (0 to 1)	1 (0 to 4)	4 (1 to 12)	
Pooled specificity 99.9% (99.7 to 99.9)	**True-negatives**	Appropriately do not receive drug treatment	965 (965 to 965)	891 (891 to 891)	693 (693 to 693)	13,392
	False-positives	Will receive unnecessary drug treatment	10 (10 to 10)	9 (9 to 9)	7 (7 to 7)	
Indirect test comparisons	There were no statistically significant differences between sensitivity or specificity results for the different test types[c]					

[a]95% CI: 95% confidence interval
[b]Values of prevalence chosen to represent low (2.5%), medium (10%), and high (30%) prevalence scenarios.
[c]Detailed estimates of indirect test comparisons can be found in Table 1.

BACKGROUND

Efforts to curb HIV infection in children have witnessed significant success. It is estimated that there was a 48% reduction in new infections amongst children (aged 0 to 14 years) between 2009 and 2014 (UNAIDS 2015). In 2016, there were fewer than 200,000 new infections amongst children attributed to the increased coverage of antiretroviral therapy (ART) to prevent mother-to-child transmission of HIV (UNAIDS 2017). Whilst much progress has been made, it is estimated that 1.5 million infants are still exposed to HIV every year. In 2015, there were 150,000 new HIV infections in infants in sub-Saharan Africa alone (UNAIDS 2015). Children infected in utero are especially at high risk of death (Becquet 2012).

World Health Organization (WHO) guidelines recommend that all HIV-infected infants and children less than five years of age be started on lifelong ART irrespective of immunological status (CD4 count) or WHO clinical stage (WHO 2015; WHO 2016). Early diagnosis of HIV infection in infants exposed to HIV is vital for starting ART promptly. The mortality of HIV-infected infants is high within the first year of life, hence the need for prompt testing, relaying of valid results, and immediate ART initiation (WHO 2013; WHO 2016). It is estimated that only 50% of HIV-infected infants are tested within the first two months of life, of whom only 40% are linked to care (Mallampati 2017). Left untreated, about 50% to 60% of HIV-infected infants die by the age of two years (Chatterjee 2011).

Available tests used to determine if a person is infected with HIV include antibody tests, p24 antigen tests, and polymerase chain reaction (PCR) tests (UNITAID 2015). The WHO recommends that PCR tests involving nucleic acid technologies (NAT) be used to confirm HIV infection in infants and children less than 18 months of age (WHO 2016). The DNA PCR test, a qualitative test to detect the presence of HIV proviral DNA, has been the most widely used for early diagnosis of HIV infection in infants and children less than 18 months of age exposed to HIV infection. Early diagnosis of HIV infection in infants and children less than 18 months of age exposed to HIV infection is also currently done using laboratory-based testing with reverse transcriptase PCR tests (RT-PCR tests) detecting HIV viral ribonucleic acid (RNA). Whole blood samples for testing are commonly collected using the dried blood spot (DBS) technique and transported to the laboratory for testing and interpretation (UNITAID 2014; UNITAID 2015; WHO 2013; WHO 2014; WHO 2016). Results can take weeks to months to be relayed back to the clinics due to poor access to central laboratories in low-resource settings, leading to delays in initiating therapy (Ciaranello 2011; UNITAID 2015). For example, in Mozambique, about 62% of HIV-exposed infants received HIV test results more than one month after sample collection in 2014 (Meggi 2017). The use of rapid diagnostic tests at or near the point-of-care (POC) can increase access to early diagnosis of HIV infection in infants and children less than 18 months of age and timely initiation of ART. POC tests are easy to use, require minimal laboratory infrastructure, and are cost-effective. They can potentially reduce patient waiting time and loss to follow-up of cases, ultimately curbing mortality (Drain 2014; UNITAID 2014; WHO 2014; WHO 2016).

Target condition being diagnosed

The target condition was the presence of HIV infection in infants and children aged 18 months of age or less. HIV is an RNA virus that infects activated CD4-positive white blood cells. On entering the white blood cells, the virus rapidly produces proviral DNA using a reverse transcriptase enzyme that converts viral RNA to DNA. This proviral DNA integrates into the host genome and remains indefinitely. At the earliest point in HIV infection, it is likely that only proviral DNA can be detected. As the virus divides within white blood cells, it releases virus particles including viral proteins (e.g. viral protein p24) and viral RNA into the blood. At this stage, both viral proteins (e.g. p24) and viral RNA can be detected in the blood, although in infants under 18 months of age viral protein detection may require denaturing of complexes formed with maternal antibodies. Patients typically seroconvert two to three weeks postinfection as they produce an antibody response to the virus. In infants, maternal antibodies may be present for up to 18 months. After seroconversion, it is likely that p24 can only be detected if complexes formed with patient antibodies are denatured. At seroconversion, RNA, DNA, and antibodies to HIV and p24 (if antibody complexes are disrupted) are all detectable (UNITAID 2014; WHO 2013; WHO 2016). There are two main types of HIV; HIV-1 and HIV-2. Compared to HIV-2, HIV-1 is more dominant and pathogenic. HIV-1 is responsible for most of the global pandemic whereas HIV-2 is most prevalent in West Africa (Deeks 2015).

Index test(s)

Nucleic acid-based tests (NAT) to detect HIV-1/HIV-2 infection include DNA PCR tests targeted to detect integrated proviral DNA and RNA RT-PCR tests that detect viral RNA. RNA RT-PCR tests may also have the potential to detect integrated proviral DNA. Point-of-care nucleic acid-based tests (POC NAT) using the RT-PCR technology have been developed to detect HIV infection in infants and children aged 18 months or less. These tests can present results qualitatively (presence or absence of viral RNA) or quantitatively (amount of viral RNA). It is not necessary to know the amount of HIV viral nucleic acid before initiating ART. In this review, we evaluated the accuracy of POC NAT tests that use the RT-PCR platform to detect the presence of HIV viral RNA in infants and children aged 18 months or less, as it is the most commonly used platform (UNITAID 2015; WHO 2010).

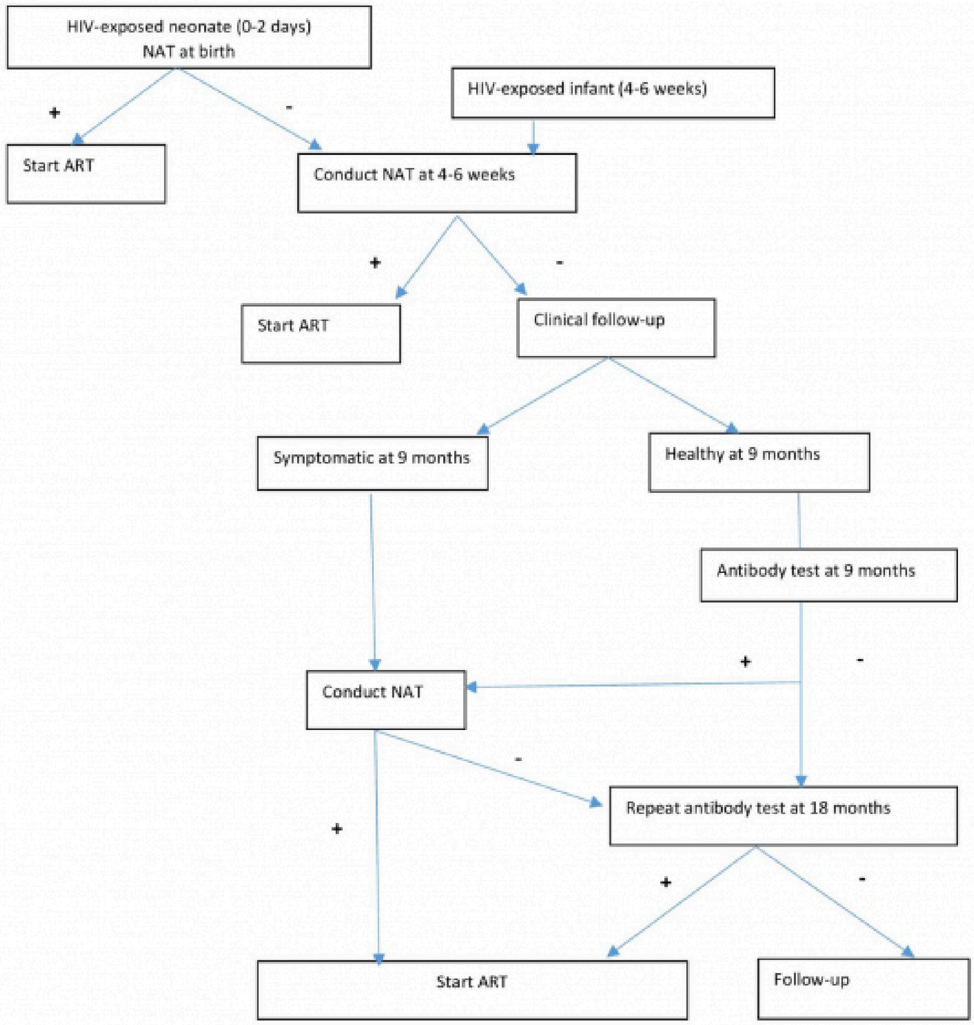
There is no universally accepted definition of POC testing (Drain 2014; UNITAID 2015). WHO defines POC tests as testing that is conducted rapidly at or near the site of clinical care of the patient with the aim to facilitate timely and cost-effective decision-making (WHO 2016). WHO also recommends that the ideal rapid test for resource-limited settings meet the ASSURED criteria (Affordable, Sensitive, Specific, User-friendly, Robust & Rapid, Equipment free, and Deliverable to end-users) (Wu 2012). However, in resource-limited settings what defines a true POC test is often blurry, as tests with POC platforms have been evaluated and implemented across a wide range of healthcare and laboratory facilities (UNITAID 2015). To maximize the utility of our review, we evaluated all forms of POC NAT tests regardless of the health facility setting in which the test was conducted.

Clinical pathway

Virological testing is regarded as the confirmatory test for HIV infection. It is recommended that the NAT test be administered to HIV-exposed newborns (aged zero to two days) or HIV-exposed infants at four or six weeks of age, and to all symptomatic or seropositive infants (positive by antibody test) at nine to 18 months to confirm HIV infection. If a NAT test is positive for HIV viral nucleic acid, the child is started on lifelong ART (see Figure 1) (WHO 2016).

The role of the POC NAT tests in this pathway will be to replace the laboratory tests used to detect HIV infection in infants and children aged 18 months or less.

Figure 1. Clinical pathway for HIV infection in infants and children ≤ 18 months of age. Abbreviations: ART: antiretroviral therapy; NAT: nucleic acid technologies.



Alternative test(s)

Alternative POC tests used to detect HIV-1/HIV-2 infection in infants and children aged 18 months or less include p24 antigen tests detecting viral protein in plasma or DBS. The p24 antigen is detectable during the acute phase of HIV infection (two to 12 weeks after exposure to HIV infection) when the virus is rapidly replicating. However, levels drop significantly after the acute phase of infection, becoming almost undetectable thereafter (UNITAID 2015). One evaluation of a prototype POC p24 antigen test in Mozambique demonstrated low sensitivity of 71.9% but a high specificity of 99% amongst 879 HIV-exposed infants (aged 28 days to 18 months) (Meggi 2017).

Serological rapid diagnostic tests (HIV antibody tests measured in blood, saliva, or urine) are not recommended for confirmatory HIV diagnosis in infants and children of 18 months of age or less as they may produce false-positive results due to the presence of maternal antibodies persisting up to 18 months of age. However, they have been recommended as a test for ruling out HIV infection in nine-month-old asymptomatic HIV-exposed infants who are not being breastfed (WHO 2016). Antibody tests are generally recommended to diagnose HIV infection in children older than 18 months and in adults. We did not evaluate these alternative tests in this review.

Rationale

Point-of-care nucleic acid-based tests (POC NAT) are being developed to detect HIV infection in infants and children aged 18 months or less in resource-limited settings. If they have a high level or acceptable accuracy, they can replace or complement laboratory-based testing platforms, as POC tests can be quicker to use and may minimize delays in initiating therapy in HIV-infected infants (Drain 2014). A POC NAT test with a high sensitivity will minimize false-negative results by detecting viral RNA in truly infected infants and children, ensuring that they are promptly initiated on ART.

This test also needs a high specificity to minimize false-positive results and unnecessary ART. The WHO recommends that HIV virological tests used to confirm HIV infection have a sensitivity of 95% or more and a specificity of 98% or more (WHO 2016). Evaluations of POC NAT tests from different manufacturers have been conducted in various geographical and healthcare settings (field and laboratory settings) and in infants and children at different ages (Dunning 2017; Hsiao 2016; Ibrahim 2017a; Jani 2014; Murray 2017; Ritchie 2016). Estimates of sensitivity range from 90% to 100%, whilst specificity varies less, with a range of 99% to 100%. A summary of accuracy estimates with added information on sources of variation in these estimates will be useful in informing decisions on the scale-up of these tests.

OBJECTIVES

To summarize the diagnostic accuracy of point-of-care nucleic acid-based tests to detect HIV-1/HIV-2 infection in infants and children aged 18 months or less exposed to HIV infection.

Secondary objectives

To investigate sources of heterogeneity in test accuracy estimates including infant/child age, sample type, test type, site of index test evaluation, geographical location, and methodological quality of the included studies.

METHODS

Criteria for considering studies for this review

Types of studies

We included any primary study that compared the results of the index test to those of a reference standard (cross-sectional, prospective, and retrospective study designs or diagnostic accuracy studies performed within randomized trials), and those that provided sufficient data to create the 2 × 2 table to calculate sensitivity and specificity.

We excluded ecological studies, studies without a reference standard or comparator, case reports and case series studies, animal or laboratory studies, reviews, discussion papers, non-research letters, commentaries, and editorials. We also excluded diagnostic case-control studies where the test performance was compared in participants with the target condition versus healthy people, as specificity will be overestimated (Macaskill 2013; Rutjes 2005).

Participants

Infants and children aged 18 months or less who were exposed to HIV infection. We did not place any limitations on type or subtype (e.g. HIV-1 or HIV-2) or limit participants by health or geographical setting.

Index tests

We included POC NAT tests that use the RT-PCR platform to detect the presence or absence of viral RNA in whole blood or plasma of infants and children aged 18 months or less. These tests could be conducted at the site of clinical care (true POC tests) or near the site of clinical care (near-POC tests) as recommended by WHO. Because POC tests have been evaluated and implemented across a wide range of public healthcare and laboratory facilities in resource-limited settings (UNITAID 2015), we included studies evaluating POC tests regardless of site of test evaluation. For example, a POC test may have been evaluated on patient blood samples in a laboratory (Hsiao 2016).

We included both commercially and non-commercially available tests. Examples of commercially available POC NAT tests include the following (UNITAID 2014; UNITAID 2015).

- Alere q Analyser and Alere q HIV-1/2 Detect (qualitative whole blood assay): detects both HIV-1 or HIV-2 in 25 µL of whole blood, which can be collected through venous collection or from capillary blood (finger or heel prick). It has a total assay time of 60 minutes. This test was recently renamed m-PIMA q HIV-1/2 Detect Assay (WHO 2020).
- Xpert HIV-1 Qualitative Assay (Cepheid): detects all HIV-1 subtypes in 100 µL of whole blood specimens.
- SAMBA I and SAMBA II HIV-1 Qualitative Tests: use 100 µL of whole blood and detect all HIV-1 subtypes. They have a total assay time of about two hours.

Target conditions

Presence or absence of HIV-1/HIV-2 infection denoted by HIV viral nucleic acids.

Reference standards

Laboratory-based virological assays to detect viral nucleic acid (HIV DNA, RNA, or total nucleic acid) on blood specimens (whole blood or DBS specimens) taken at the same time (within 24 hours) as the sample for POC NAT tests. The most widely used laboratory test is the qualitative DNA PCR molecular test. This test detects the presence of HIV-1 DNA and presents the results in a binary format: infection or no infection. Two laboratory platforms, the Roche COBAS TaqMan HIV-1 Qualitative Test (v1.5 or 2) and the Abbott RealTime Qualitative HIV-1 (m2000), are considered gold standards, although the Roche test has a superior sensitivity (UNITAID 2014). The Roche test detects HIV-1 DNA and RNA from whole blood or DBS specimens and has a total assay time of five to six hours. The Abbott test can detect HIV-1 quantitatively or qualitatively. The Abbott RealTime qualitative test is based on the RT-PCR technology and detects HIV-1 in plasma or DBS specimens with a total assay time of 5.5 to 8 hours (UNITAID 2015). WHO does not recommend the tie-breaker approach, where the results of a third administered test are used to resolve discrepant test results; there could be a risk of false-positive results when the tie-breaker test is used to rule in HIV infection (Kosack 2017). We thus disregarded the results of the tie-breaker test in cases where there was a discrepancy between the index test and the reference test, and the discrepant sample is retested with another reference test (tie-breaker test) (Ritchie 2014). When the tie-breaker reference test rules in HIV infection, the specificity of the index test may be overestimated.

Search methods for identification of studies

Electronic searches

We searched the following databases from 1990 onwards, as POC tests for HIV were not researched before then, with no language or publication status restriction until 1 and 2 February 2021. We also searched conference websites, tracked reference lists of included studies and relevant systematic reviews, and consulted experts for potentially relevant studies.

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (January 1990 to 2 February 2021).
- MEDLINE Ovid (1990 to 1 February 2021).
- Embase Ovid (1990 to 1 February 2021).
- LILACS (Latin American and Caribbean Health Sciences Literature database) (searched 2 February 2021).
- Web of Science (Core Collection, includes Science Citation Index Expanded (SCI-EXPANDED) and Conference Proceedings Citation Index - Science (CPCI-S)) (searched 2 February 2021).

The search strategies for the above databases are shown in Appendix 1.

Searching other resources

We searched the following sources for additional, unpublished, or ongoing studies.

- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/) (searched 2 February 2021).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/) (searched 2 February 2021).
- WHO Global Index Medicus (searched 2 February 2021).
- Conference websites from 2014 based on evidence that mean time to publication rates of conference presentations is between two and four years (Abzug 2014; Mutlu 2015). Conferences include: Conference on Retroviruses and Opportunistic Infections (www.croiconference.org); International AIDS Society (www.iasociety.org/Conferences), and African Society for Laboratory Medicine (www.aslm.org/).

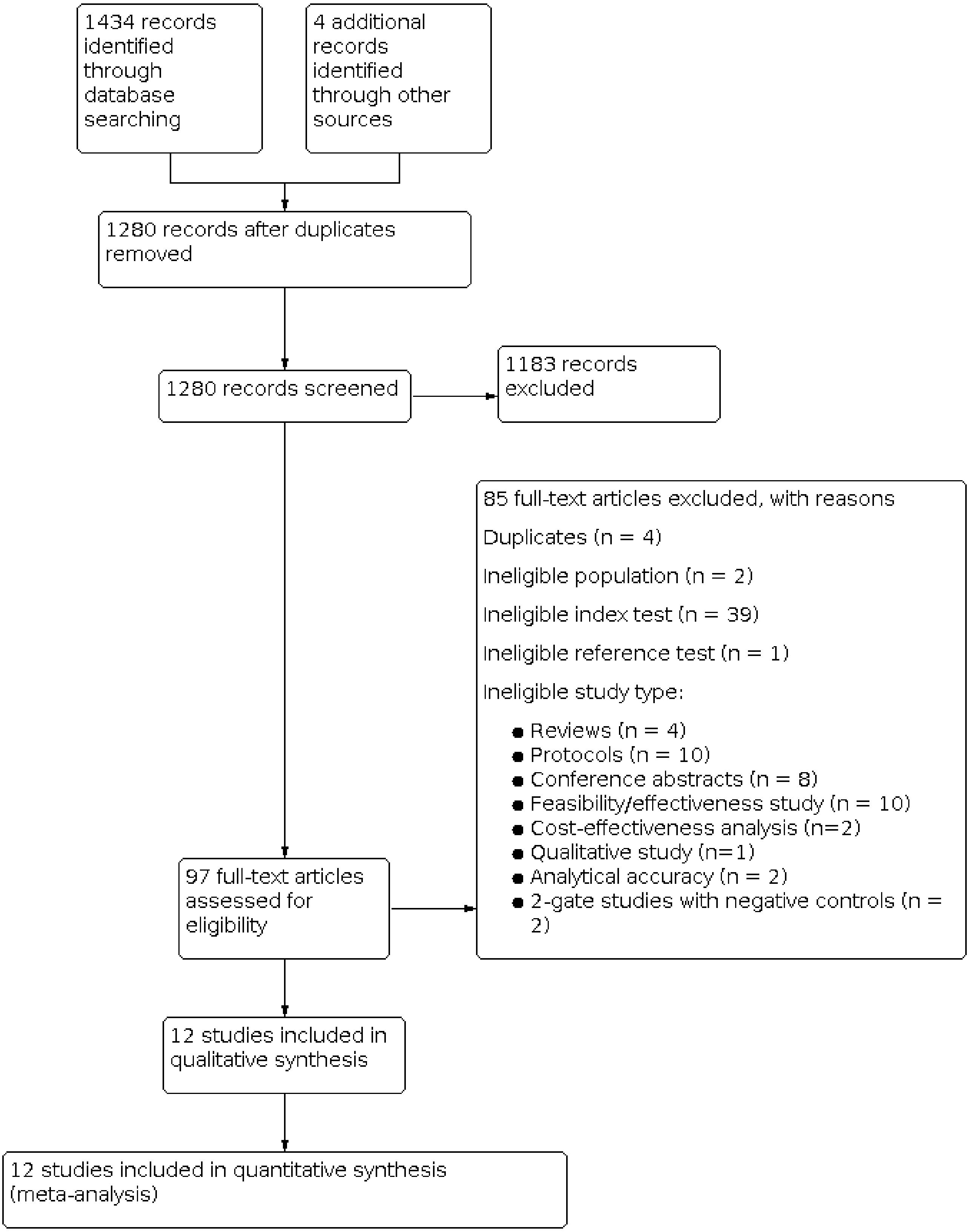
We also tracked reference lists of included studies and relevant systematic reviews and consulted the WHO HIV Department for potentially relevant studies.

Data collection and analysis

Selection of studies

Two review authors (EO and FG) independently screened the titles and abstracts of the search results to identify eligible articles, removing reports that were obviously not relevant or that were duplicates. The two review authors (EO and FG) then independently assessed the full texts of journal articles or conference proceedings for eligibility based on our a priori inclusion criteria. Any disagreements were resolved by consensus. We documented our justifications for excluding articles from the review in the Characteristics of excluded studies table. Details of the included studies are presented in the Characteristics of included studies table. The study selection process is illustrated in a PRISMA flow diagram (see Figure 2).

Figure 2. Study flow diagram.



Data extraction and management

We extracted the following information on study characteristics: study design, demographic and participant characteristics, methods of collecting blood specimen, index test and reference standard characteristics, test cut-off and performance, and accuracy results (true-positive, false-positive, false-negative, and true-negative (Appendix 2). In the case of unclear accuracy data, we contacted primary authors of included studies for clarification.

Two review authors (EO and FG) independently performed data extraction. Any disagreements were resolved by discussion, and all decisions were documented.

Assessment of methodological quality

We used QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool to assess the risk of bias and applicability concerns of the included studies (Whiting 2011). We tailored the tool in line with the context of our review question (Appendix 3). Two review authors (EO and FG), using a predesigned and pretested form, independently assessed risk of bias in the included studies. Any disagreements were resolved by consensus.

Statistical analysis and data synthesis

The unit of analysis was the participant. For each study, we obtained binary or dichotomous data (infection or no infection) from these tests, which we fed into the 2 × 2 table to calculate sensitivity and specificity of POC NAT tests compared with laboratory reference testing.

We conducted preliminary exploratory analyses by plotting estimates of sensitivity and specificity from each study on forest plots and in receiver operating characteristic (ROC) space. These analyses enabled visual assessment of the variation between studies, and will also facilitate investigations of heterogeneity exploring the effect of certain characteristics on test performance.

In the overall meta-analyses we analysed accuracy across all types and manufacturers of tests combined. We used the bivariate meta-analysis model to estimate sensitivity and specificity using the xtmelogit command in STATA. The bivariate model with random-effects accounts for within-study variability and correlation of sensitivity and specificity. The model uses study-specific estimates of the true-positive rate (sensitivity) and the false-positive rate (1 minus specificity) to estimate a mean operating point (Macaskill 2013; Reitsma 2005).

We only conducted indirect test comparisons, as no studies evaluated more than one test on the same patients. For meta-analyses with fewer than 12 evaluations, bivariate models did not converge, as specificity was 100% in most included studies, except for two studies, where it was 99%. Where the bivariate models did not converge, we undertook a univariate random-effects meta-analysis of sensitivity and specificity. We calculated the mean difference in sensitivity giving 95% confidence interval (CI) for difference and P value). When the univariate method failed because there were zero or one or two false-positives, we combined patient test results as if from a single study and computed the proportion and 95% CI using the binomial exact method (Clopper 1934).

We performed descriptive analyses using Review Manager 5 (Review Manager 2020), and fitted the bivariate model using STATA 14.2 (STATA 2017).

Investigations of heterogeneity

We investigated the following sources of heterogeneity where there were sufficient data: sample type (DBS versus fresh whole blood sample), infant/child age (at birth, six weeks or less, 12 months or less, and 18 months or less), test type (for each manufacturer), and site of index test evaluation (field versus laboratory settings). We fitted simplified univariable models for sensitivity and specificity separately using a random-effects model, as the bivariate models did not converge to give a model estimate. When the univariate method failed because there were zero or one or two false-positives, we combined patient test results as if from a single study and computed the proportion and 95% CI using the binomial exact method (Clopper 1934).

Sensitivity analyses

We used sensitivity analyses to explore the effect of potentially influential studies and study quality. We performed sensitivity analysis excluding studies based on risk of bias (excluding those with high risk of bias in QUADAS-2 domains (participant selection, index test, reference standard, flow and timing)). We did not restrict analysis to studies conducted in sub-Saharan Africa as stated a priori, as all studies were conducted in this geographical region. The sensitivity analysis restricted to studies at low concern for applicability corresponded to studies conducted in a field setting, so results from the subgroup analysis of field setting was identical to this planned sensitivity analysis. One study had a low sensitivity of 83% (Opollo 2018), compared to the rest, which had sensitivity estimates ranging from 93% to 100%. Another study had a population inclusion criteria of ≤ 24 months and not ≤ 18 months (Hsiao 2016), although a small proportion (29%) of included participants were aged between > 14 weeks and < 24 months. We excluded these studies from the overall meta-analysis to check the effect on the summary estimates.

Assessment of reporting bias

We did not assess reporting bias, as there is no consensus on recommended methods of evaluating publication bias for Diagnostic Test Accuracy reviews (Macaskill 2013).

Assessment of the strength of the evidence

We summarized the main findings from the review, reporting the numbers of true-positives, true-negatives, false-positives, and false-negatives per 1000 tested in a summary of findings table (Bossuyt 2013). GRADE for Diagnostic Test Accuracy reviews is still under development (Gopalakrishna 2014). Rather than following any formal process for downgrading the evidence, we planned to fully describe the following concepts, which constitute an assessment of the strength of the evidence.

- Precision of study estimates.
- Heterogeneity in study findings.
- Risk of bias.
- Concerns about applicability.
- Indirect test comparisons.

These issues cover the key domains of GRADE (except publication bias) and would allow the evidence to be included in a GRADE assessment should a guideline developer wish to do so.

RESULTS

Results of the search

Our search yielded a total of 1438 records, of which four were found through additional searches. We screened 1280 titles and abstracts and retrieved 97 full texts. We assessed the full texts and excluded 85 articles and included 12 studies in the systematic review and meta-analyses. The search results are shown in Figure 2.

Included studies

We identified a total of 12 studies (15 evaluations, 15,120 participants). Eleven studies had a cross-sectional design, whilst the study design of one study was unclear (Ondiek 2017a). For details of the included studies, see Characteristics of included studies.

Excluded studies

We excluded 85 articles after full-text review. For details of the excluded studies, see Characteristics of excluded studies. In summary four were duplicates; two were primary studies with ineligible populations; 39 studies had ineligible index tests (not POC NAT); one study had an ineligible reference test; and 39 studies were ineligible study types (including reviews (n = 4), protocols (n = 10), conference abstracts (with no accuracy data) (n = 8), non-accuracy studies (n = 13), studies that evaluated analytical accuracy measures (n = 2), or two-gate accuracy studies with negative controls (n = 2)).

Methodological quality of included studies

The results of our quality appraisal of the 12 included studies (15 evaluations) are summarized in Figure 3 and Figure 4. We evaluated these studies for risk of bias in the following QUADAS-2 domains (Whiting 2011): participant selection, index test, reference standard, and participant flow. The risk of bias assessments were largely low or unclear across the four domains. We judged one study, Meggi 2017, to have a high risk of bias for the patient selection domain. This study had a strict exclusion criteria with a risk for inappropriate exclusions. Those with serious medical conditions, delivery complications, who were born through Caesarean section, who were born to mothers with mental illness, and those not born at the participating health facilities were excluded. It was also unclear if a consecutive or random sample of patients was enrolled.

Figure 3. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

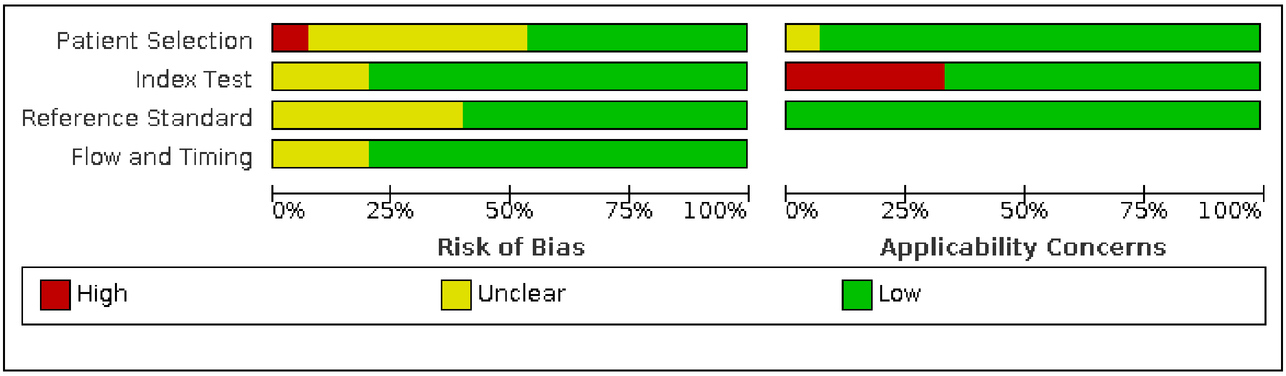
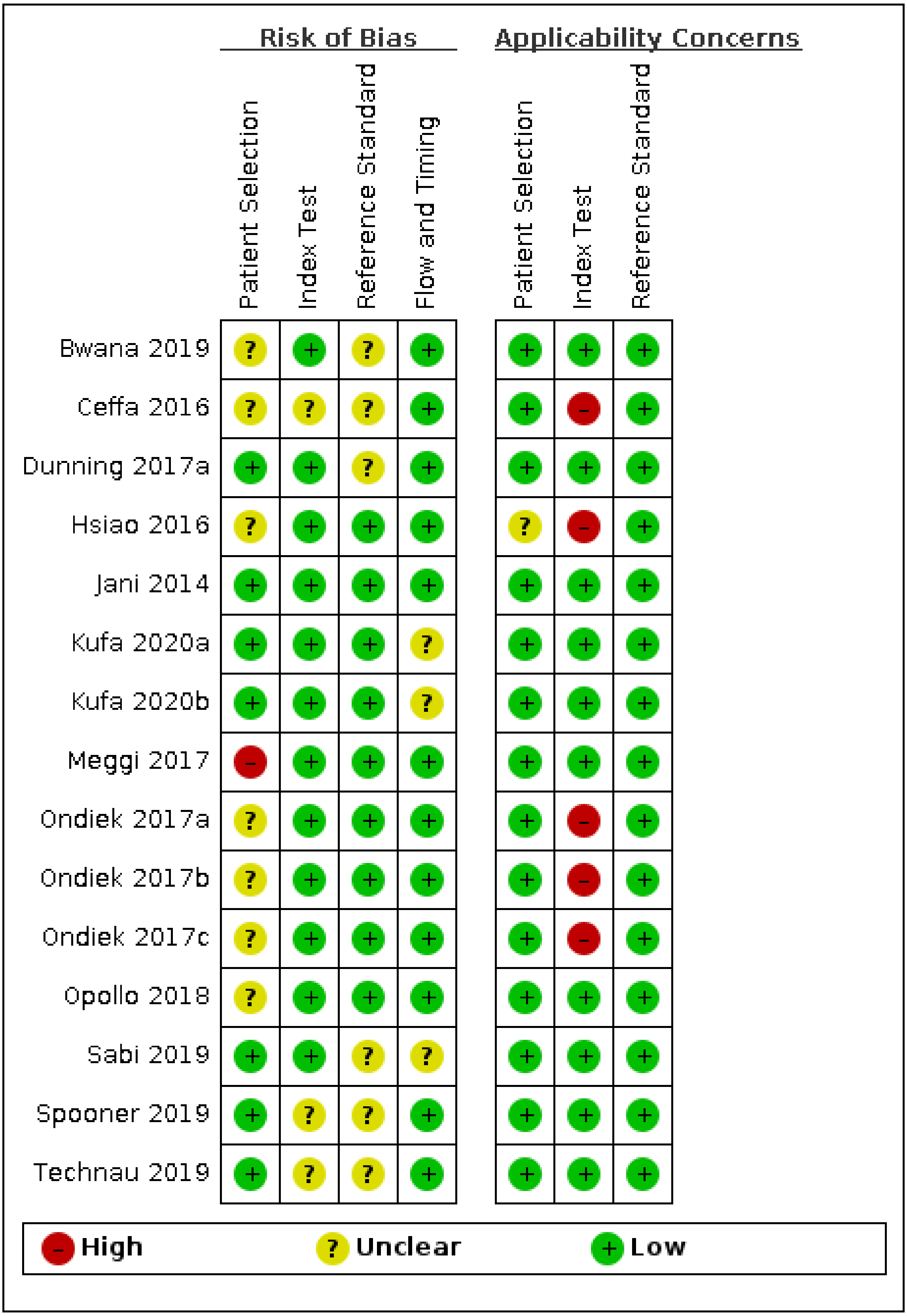


Figure 4. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.



We had some concerns regarding applicability for five evaluations. The studies conducted the POC NAT tests in a laboratory setting with trained technicians. These tests included Alere (Hsiao 2016), Cepheid Xpert (Ceffa 2016), and SAMBA (Ondiek 2017a; Ondiek 2017b; Ondiek 2017c).

Findings

A summary of the main findings is provided in Summary of findings 1.

We included 12 studies which completed 15 evaluations; one study completed an evaluation of one test type in three different settings (Ondiek 2017a; Ondiek 2017b; Ondiek 2017c), and one study completed an evaluation of two different test types (Kufa 2020a; Kufa 2020b). A total of 15 evaluations of the POC NAT were performed with a total of 15,120 individuals. All evaluations were conducted in sub-Saharan Africa. These evaluations were described in articles published between the years of 2014 and 2020.

Six evaluations assessed the accuracy of the POC NAT at birth; the remaining evaluations assessed the accuracy of the POC NAT at various age cutoffs (≤ 12 months (n = 3), ≤ 18 months (n = 5), ≤ 24 months (n = 1)). We included the study with a cutoff of ≤ 24 months because a large proportion of infants (n = 784, 71%) were tested between birth and 14 weeks, with the rest (n = 314, 29%) tested after 14 weeks (Hsiao 2016). The proportion of participants tested between 14 weeks and 18 months was not clearly reported in this study.

Ten evaluations were field evaluations of the POC NAT test, whereas five were evaluations of the POC NAT tests in a centralized laboratory setting. Eleven evaluations used whole blood, and 4 dried whole blood spot. The test types evaluated as POC NAT tests included Alere q HIV-1/2 qualitative test (recently renamed m-PIMA q HIV-1/2 Detect qualitative test, n = 6), Xpert HIV-1 qualitative test (n = 6), and SAMBA HIV-1 qualitative test (n = 3). Twelve evaluations used the Roche COBAS AmpliPrep/COBAS Taq-Man (CAP/CTM) HIV-1 Qualitative test as the reference standard; one evaluation used the Abbott Real Time HIV-1 Qualitative assay as the reference standard (Ceffa 2016); and the reference standard was not clearly stated (central laboratory testing) in two evaluations (Kufa 2020a; Kufa 2020b). The forest plot (Figure 5) and summary receiver operating characteristic (SROC) plot (Figure 6) for the POC NAT revealed little heterogeneity for estimates of sensitivity. Specificity estimates were similar.

Figure 5. Forest plot outlining the sensitivity and specificity of evaluations of POC NAT early infant diagnosis.

Study	TP	FP	FN	TN	Test type	Age	Location	Sensitivity (95% CI)	Specificity (95% CI)
Dunning 2017a	13	0	1	380	Alere	<12mths	Field	0.93 [0.66, 1.00]	1.00 [0.99, 1.00]
Bwana 2019	258	2	7	634	Xpert	<12mths	Field	0.97 [0.95, 0.99]	1.00 [0.99, 1.00]
Ondiek 2017b	100	3	5	203	Samba	<12mths	Lab	0.95 [0.89, 0.98]	0.99 [0.96, 1.00]
Jani 2014	64	1	1	761	Alere	<18mths	Field	0.98 [0.92, 1.00]	1.00 [0.99, 1.00]
Opollo 2018	25	2	5	889	Xpert	<18mths	Field	0.83 [0.65, 0.94]	1.00 [0.99, 1.00]
Ondiek 2017a	200	1	3	131	Samba	<18mths	Lab	0.99 [0.96, 1.00]	0.99 [0.96, 1.00]
Ondiek 2017c	23	0	1	75	Samba	<18mths	Lab	0.96 [0.79, 1.00]	1.00 [0.95, 1.00]
Ceffa 2016	92	0	0	104	Xpert	<18mths	Lab	1.00 [0.96, 1.00]	1.00 [0.97, 1.00]
Hsiao 2016	192	2	9	832	Alere	<24mths	Lab	0.96 [0.92, 0.98]	1.00 [0.99, 1.00]
Meggi 2017	33	0	0	1827	Alere	birth	Field	1.00 [0.89, 1.00]	1.00 [1.00, 1.00]
Spooner 2019	5	0	0	435	Alere	birth	Field	1.00 [0.48, 1.00]	1.00 [0.99, 1.00]
Kufa 2020a	60	18	7	4163	Xpert	birth	Field	0.90 [0.80, 0.96]	1.00 [0.99, 1.00]
Sabi 2019	588	0	0	10	Xpert	birth	Field	1.00 [0.99, 1.00]	1.00 [0.69, 1.00]
Technau 2019	30	2	0	2097	Xpert	birth	Field	1.00 [0.88, 1.00]	1.00 [1.00, 1.00]
Kufa 2020b	6	0	0	820	mpima(Alere)	birth	Field	1.00 [0.54, 1.00]	1.00 [1.00, 1.00]

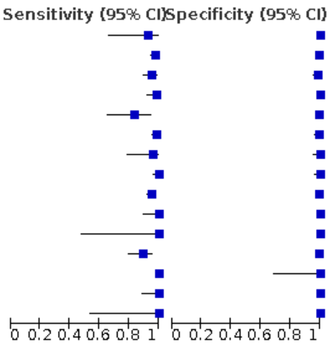
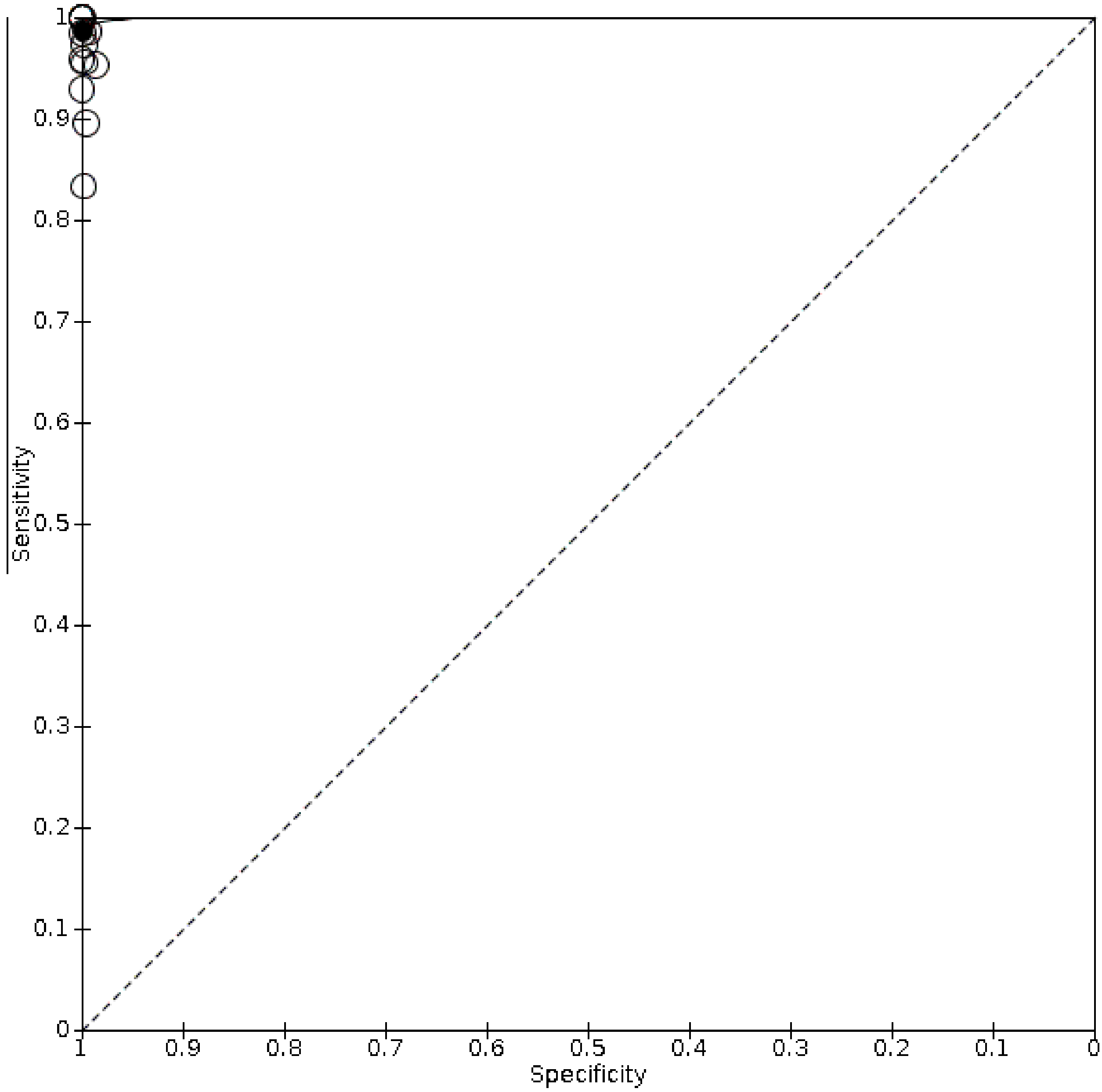


Figure 6. Summary receiver operating characteristic (ROC) plot of POC NAT early infant diagnosis as determined by the bivariate model. The solid point represents the summary estimate for sensitivity and specificity.



A. Primary analysis, POC NAT for detection of HIV infection

Sensitivity estimates ranged from 83% to 100% for the 15 evaluations (Figure 5). Opollo 2018 (sensitivity 83%) was conducted amongst mother/guardian-infant pairs attending expanded programmes of immunization (EPI) services at selected clinics and hospital. Specificity estimates ranged from 99% to 100%, although most estimates (n = 13) were 100%.

POC NAT pooled sensitivity and specificity (95% CI) against laboratory tests were 98.6% (96.1 to 99.5) (15 evaluations, 1728 participants) and 99.9% (99.7 to 99.9) (15 evaluations, 13,392 participants).

B. Investigating sources of heterogeneity

A summary of our investigation into variation in sensitivity and specificity is shown in Table 2.

Subgroup analysis

We investigated the following sources of heterogeneity where data were sufficient: age (birth, ≤ 12 months, ≤ 18 months); test type (Xpert, Alere, SAMBA); location (lab versus field); and sample (dried blood versus fresh sample). For investigation of heterogeneity, we only pooled estimates for sensitivity, as most evaluations (n = 13) had a specificity of 100%, and two evaluations had a specificity of 99% (Ondiek 2017a; Ondiek 2017b). Where we could not pool estimates (specificity for covariates, age, test type, location, and sample type), we combined the participants across the studies and computed the proportion and 95% CI using the binomial exact method. These pooled estimates for specificity thus ranged from 99.0% to 99.9% (Table 2).

Age

Pooled sensitivity (95% CI) at birth, ≤ 12 months, and ≤ 18 months were 99.0% (98.0 to 100.0), 96.6% (94.3 to 98.0) and 97.9% (91.9 to 99.5), respectively. Sensitivity was statistically different between birth and ≤ 12 months (difference sensitivity (95% CI) 3.4% (1.5 to 5.2)). Sensitivity was not statistically different between birth and ≤ 18 months (difference sensitivity (95% CI) 2.1% (−0.8 to 5.0)) and between ≤ 12 months and ≤ 18 months (difference sensitivity (95% CI) −1.3% (−4.7 to 2.2)). Specificity results were as follows: at birth 99.8% (99.7 to 99.9); at ≤ 12 months 99.6% (99.0 to 99.9); and at ≤ 18 months 99.8% (99.5 to 99.9).

Test type

The pooled sensitivity (95% CI) for the index tests Xpert, Alere, and SAMBA was 99.2% (88.1 to 100), 96.6% (94.0 to 98.1), and 97.3% (94.4 to 98.7), respectively. Specificity results were as follows: Xpert 99.7 (99.5 to 99.8), Alere 99.9% (99.8 to 100), and SAMBA 99.0% (97.5 to 99.7).

Location

The pooled sensitivity (95% CI) was 97.4% (94.8 to 98.7) for index tests conducted in laboratory settings and 98.7% (93.4 to 99.8) for index tests conducted in a field setting (at or near patient site). There was no statistically significant difference in sensitivity between settings: lab minus field was −1.3% (−4.1 to 1.5). Specificity results were as follows: lab 99.6% (99.0 to 99.8) and field 99.8% (99.7 to 99.9).

Sample

The pooled sensitivity (95% CI) was 98.4% (94.9 to 99.5) for tests done on fresh whole blood samples and 97.7% (89.4 to 99.5) for tests done on dried whole blood samples. There was no statistically significant difference in sensitivity between sample types: dried minus fresh was 0.7% (−4.8 to 3.4). Specificity results were as follows: fresh whole blood 99.8% (99.7 to 99.8) and dried whole blood spot 99.8% (99.5 to 99.9).

Sensitivity analysis

When studies with high risk of bias in any domain were excluded (Meggi 2017), POC NAT pooled sensitivity and specificity (95% CI) were similar to the overall meta-analysis: 98.4% (95.6 to 99.4) and 99.8% (99.7 to 99.9), respectively. When we excluded Opollo 2018 due to outlier results, the pooled sensitivity of POC NAT was 98.9% (95% CI 96.7 to 99.6), and pooled specificity 99.9% (95% CI 99.7 to 99.9) was also similar to the overall meta-analysis. When we excluded Hsiao 2016 due to its inclusion of a population ≤ 24 months, the pooled sensitivity of POC NAT was 98.6% (95% CI 97.7 to 99.2), and pooled specificity 99.9% (95% CI 99.8 to 99.9) was also similar to the overall meta-analysis.

C. Indirect test comparisons

There were no statistically significant differences between sensitivity or specificity results for different test types. Differences in sensitivity were as follows: Xpert difference in sensitivity 2.6% (−0.3 to 5.5) compared to Alere and 2.0% (−0.1 to 4.9) compared to SAMBA; difference in sensitivity of SAMBA and Alere 0.7% (−2.1 to 3.5) (Table 1).

DISCUSSION

This review evaluated the diagnostic accuracy of POC NAT tests in detecting HIV-1/HIV-2 infection in infants and children up to 18 months of age in comparison with a reference standard of laboratory NAT RT-PCR or total nucleic acid testing. It summarizes the literature published between the years 2014 to 2020 (12 studies, 15 evaluations).

Summary of main results

We identified a total of 12 studies (15 evaluations, 15,120 participants). All studies were conducted in sub-Saharan Africa. The ages of included infants and children in the evaluations were as follows: at birth (n = 6), ≤ 12 months (n = 3), ≤ 18 months (n = 5), and ≤ 24 months (n = 1). Only five studies (six evaluations) evaluated the accuracy of POC NAT tests at birth. There were 10 field evaluations and five laboratory evaluations of the POC NAT tests. The POC NAT tests evaluated included Alere q HIV-1/2 Detect qualitative test (n = 6), Xpert HIV-1 qualitative test (n = 6), and SAMBA HIV-1 qualitative test (n = 3).

POC NAT pooled sensitivity and specificity (95% CI) against laboratory reference standard tests were 98.6% (96.1 to 99.5) and 99.9% (99.7 to 99.9).

In a hypothetical cohort of 1000 children ≤ 18 months where 100 have HIV infection, 100 will receive a positive result from the POC NAT test, of which one will not have the infection (false-positive result), and 900 will receive a negative result from the POC NAT test, of which one will indeed have the infection (false-negative result).

Risk of bias in the included studies was mostly low or unclear. Three studies (five evaluations) had high concerns regarding applicability for the index test, as they were conducted as laboratory evaluations but there was no statistically significant difference (−1.3% (−4.1 to 1.5)) in sensitivity (95% CI) between settings; lab 97.4% (94.8 to 98.7) minus field (98.7% (93.4 to 99.8). Specificity (95% CI) results were similar: lab 99.6% (99.0 to 99.8) and field 99.8% (99.7 to 99.9).

Strengths and weaknesses of the review

Our findings were based on a comprehensive literature search in electronic databases and the grey literature. We contacted some authors for clarification on study inclusion, and also consulted with experts on the comprehensiveness and applicability of our findings. In addition, our findings are similar to a pooled analysis evaluating the field performance of POC tests for early infant diagnosis (Xpert and Alere) from six different African countries (Carmona 2016). Pooled sensitivity and specificity (95% CI) were 99.92% (99.74 to 99.99) and 99.92% (99.74 to 99.99%) for Xpert, and 99.07% (95.48 to 99.95) and 99.94% (99.72 to 100) for Alere q HIV-1/2. We only pooled estimates of sensitivity for test type in our review. Our review demonstrated pooled estimates for sensitivity (95% CI) for different test types as follows: Xpert 99.2% (88.1 to 100.0); Alere 96.6% (94.0 to 98.1); and SAMBA 97.3% (94.4 to 98.7).

We note a number of limitations to our review. Our assessment of risk of bias across the four domains was largely unclear due to incomplete reporting of study methods in the publications.

Adhering to the standards for reporting of diagnostic accuracy studies (Bossuyt 2015), especially for reporting study design, participants, and test methods, would give a clearer assessment of risk of bias. The WHO recommended pathway (Figure 1) recommends testing with NAT at different time points ≤ 18 months (at birth, 4 to 6 weeks, and 9 months) to determine eligibility for ART. The included studies did not specifically to address accuracy at 4 to 6 weeks or 9 months, although with results at birth and ≤ 12 months were very similar. Five evaluations were conducted in a laboratory setting of the POC NAT tests and were not evaluations at or near the patient as per our review's question. Nonetheless, as reported in the Results, there was minimal impact on the results of the review, as there was no statistically significant difference in sensitivity between lab and field settings. Specificity estimates were also similar.

Applicability of findings to the review question

The findings of our review were applicable to the review question with regard to the population included and the reference standard. The included populations were largely within our inclusion criterion of ≤ 18 months. The reference standards were the tests mostly used with laboratory-based

platforms. In addition, all studies were carried out in sub-Saharan Africa, making the results highly applicable for use in endemic communities where disease control programs are often targeted. There were some concerns regarding applicability for the index test, as one-third of included evaluations were not true POCs but were tests with POC platforms evaluated in a laboratory setting. However, there is no universally accepted definition of POC testing (Drain 2014; UNITAID 2015), and in resource-limited settings what defines a true POC test is often blurry, as tests with POC platforms have been evaluated and implemented across a wide range of healthcare and laboratory facilities (UNITAID 2015).

AUTHORS' CONCLUSIONS

Implications for practice

Point-of-care nucleic acid-based testing (POC NAT) has a high sensitivity and specificity to detect or exclude HIV-1/HIV-2 infection in infants and children ≤ 18 months compared to laboratory-based viral assays. There was also no difference in estimates of sensitivity and specificity in evaluations of the POC NAT tests conducted in the field compared to the POC NAT evaluations in the laboratory. These tests could therefore complement or replace laboratory-based viral assays.

Implications for research

Larger, prospective studies are needed to evaluate the diagnostic accuracy of POC NAT in the field at point of care. Inclusion of some laboratory evaluations of the POC NAT test in this review contributed indirect evidence, which raised some applicability concerns. We also recommend more studies evaluating the accuracy of POC NAT in the youngest ages (six weeks and earlier). More studies evaluating the impact of POC NAT tests compared to standard of care (laboratory tests) using randomized trials in real-life settings or other study designs for test impact evaluations will be important to assess the real benefit of replacing laboratory-based viral assays (Schumacher 2016). Future studies should aim to address the questions of whether time to diagnosis, time to treatment, morbidity, and mortality are reduced by POC NAT tests and further emphasize the question of the risk of a POC test versus a laboratory-based viral assay. For example, Jani 2014 was a cluster-randomized trial that compared POC NAT test to laboratory standard-of-care testing on the proportion of HIV-infected infants initiating antiretroviral therapy as well as the time to initiation on antiretroviral therapy.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bwana 2019

Study characteristics			
Patient Sampling	Both the qualitative and the quantitative studies of the performance of the GeneXpert platform were cross-sectional evaluations of samples obtained from facilities across the country.		
Patient characteristics and setting	HIV-exposed infants from sites across the country; field evaluation in Kenya		
Index tests	Xpert HIV-1 qualitative (Cepheid, Sunnyvale, CA, USA) on fresh whole blood samples - dried blood spot (DBS) samples, in field evaluations		
Target condition and reference standard(s)	HIV-1 infection; Roche CAP/CTM		
Flow and timing	In field sites, two DBS filter papers were collected from infants. The contents of the vial were then added into the Xpert HIV-1 Qual test cartridge and loaded onto the GeneXpert machine. Results were observed and recorded after 90 minutes. The secondDBS filter paper was shipped to the reference lab and tested on the Roche CAP/CTM platform according to manufacturer’s instructions as previously described		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	

Bwana 2019 *(Continued)*

Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		Low risk	

Ceffa 2016

Study characteristics	
Patient Sampling	Study was conducted in the DREAM laboratory in Blantyre, Malawi, where samples from exposed newborns ≤ 18 months collected at various health centres in different districts (Blantyre, Balaka, Machinga, and Mangochi) were centralized for analysis.
Patient characteristics and setting	Exposed newborns ≤ 18 months. Study was conducted in the DREAM laboratory in Blantyre, Malawi.
Index tests	Xpert HIV-1 qualitative test (Cepheid); done in laboratory; fresh whole blood samples on DBS collected from capillaries

Ceffa 2016 *(Continued)*

Target condition and reference standard(s)	HIV-1 infection, Abbott Real Time HIV-1 qualitative assay		
Flow and timing	Samples tested in the lab		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		

Ceffa 2016 *(Continued)*

Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		Low risk	

Dunning 2017a

Study characteristics	
Patient Sampling	HIV-exposed children under 1 year of age. Consecutive HIV-exposed neonates undergoing routine early infant diagnosis testing at a large maternity hospital and a primary care clinic received both laboratory-based HIV polymerase chain reaction testing per local protocols and a point-of-care test.
Patient characteristics and setting	HIV-exposed children under 1 year of age, 2 public sector health facilities in Cape Town, South Africa (a secondary-level obstetric hospital and a primary-level midwife obstetric unit)
Index tests	Alere q 1/2 Detect (Alere Technologies GmbH, Jena, Germany); fresh whole blood samples collected from veins
Target condition and reference standard(s)	HIV-1; Roche Cobas AmpliPrep/Cobas TaqMan (CAP/CTM) HIV-1 qualitative assay
Flow and timing	Consecutive infants were selected for HIV testing on both laboratory-based assays and POC assays in parallel.
Comparative	
Notes	

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		

Dunning 2017a *(Continued)*

If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		Low risk	

Hsiao 2016

Study characteristics	
Patient Sampling	Laboratory-based evaluation. Samples from HIV-exposed children under 2 years of age undergoing routine HIV PCR testing in Western Cape province of South Africa between December 2013 and August 2014 were used for this evaluation. Samples came from children enrolled in various levels of paediatric care ranging from routine EID programme in primary care clinics to neonates delivered at maternity hospitals and specialist paediatric services.
Patient characteristics and setting	Samples from HIV-exposed children under 2 years of age; independent laboratory-based evaluation in Cape Town, South Africa. Our review question focused on infants and children ≤ 18 months. This study included 29% children > 14 weeks. It is unclear if this proportion included children between 18 and 24 months.
Index tests	Alere q HIV-1/2 Detect system (Alere Healthcare, Waltham, MA, USA); done in laboratory; whole blood specimen collected via heel prick/venepuncture

Hsiao 2016 *(Continued)*

Target condition and reference standard(s)	HIV-1; Roche Cobas AmpliPrep/Cobas TaqMan (CAP/CTM) HIV-1 qualitative assay (Roche Diagnostics, Branchburg, NJ, USA)		
Flow and timing	Following local practice, infant Ethylenediamine tetraacetic acid (EDTA) specimens (200 to 500 µL) were collected through heel prick or venepuncture at healthcare facilities, and whole blood samples were transported to the Groote Schuur Hospital laboratory of the National Health Laboratory Services (GSH-NHLS), where routine EID PCR was conducted. Whole blood samples were transported and stored at 4 °C and tested within 72 hours of blood draw.		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	

Hsiao 2016 *(Continued)*

Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		Low risk	

Jani 2014

Study characteristics	
Patient Sampling	POC and laboratory Nucleic amplification test (NAT) Early Infant Diagnosis tests were conducted on matched blood samples collected from 827 HIV-exposed infants ≤ 18 months who were enrolled consecutively at 4 periurban primary health clinics and the central hospital in Maputo.
Patient characteristics and setting	HIV-exposed infants ≤ 18 months; primary health clinics in Mozambique
Index tests	Alere Q NAT device (Alere Technologies, Jena, Germany); fresh whole blood samples collected via heel prick as Dried Blood Spot (DBS) samples
Target condition and reference standard(s)	HIV-1; Roche COBAS AmpliPrep/COBAS TaqMan (CAP/CTM 96) HIV-1 qualitative test (Roche Molecular Diagnostics, Branchburg, NJ, USA)
Flow and timing	Specimens were dried overnight at room temperature before being sent to the laboratory. Samples were stored in the laboratory for up to 1 week before being tested using the Roche COBAS AmpliPrep/COBAS TaqMan (CAP/CTM 96).
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Jani 2014 *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Kufa 2020a

Study characteristics	
Patient Sampling	Prospective study: to be eligible for enrolment and specimen collection for the study, women living with HIV (WLHIV) and/or their infants had to be admitted in labour or postnatal wards and be willing to provide verbal consent. For both WLHIV and infants, 2 specimens were collected – 1 for POC and the other for Central Laboratory Testing.

Kufa 2020a *(Continued)*

Patient characteristics and setting	Newborn infants to WLHIV; 4 high-volume tertiary obstetric units in Gauteng, South Africa		
Index tests	Xpert HIV-1 qualitative test; field at POC		
Target condition and reference standard(s)	HIV-1/HIV-2; central laboratory testing (Roche and Abbott)		
Flow and timing	Following verbal consent and pretest counselling, two samples were collected from each pregnant Women living with HIV (WLHIV) and HIV-exposed infant.For infants, two microtainer EDTA tubes (each with 250µl blood) for parallel POC testing and CLT were requested. Alternatively, one 250µl EDTA specimen for POC testing and one dried blood spot card, with at least three 70µl spots, for CLT were requested. Specimens were collected by doctors and nurses as part of their routine duties.POC EID testing was conducted using either the Xpert™ HIV-1 Qual or the m-PIMA HIV-1/2 Detect assays		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Kufa 2020a *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		Unclear risk	

Kufa 2020b

Study characteristics	
Patient Sampling	Prospective study: to be eligible for enrolment and specimen collection for the study, WLHIV and/or their infants had to be admitted in labour or postnatal wards and be willing to provide verbal consent. For both WLHIV and infants, 2 specimens were collected – 1 for POC and the other for CLT.
Patient characteristics and setting	Newborn infants to WLHIV; 4 high-volume tertiary obstetric units in Gauteng, South Africa
Index tests	m-PIMA HIV-1/2 Detect assay; field at POC
Target condition and reference standard(s)	HIV-1/HIV-2; centralized laboratory testing (Roche and Abbott)
Flow and timing	Following verbal consent and pretest counselling, two samples were collected from each pregnant Women living with HIV (WLHIV) and HIV-exposed infant.For infants, two microtainer EDTA tubes (each with 250µl blood) for parallel POC testing and CLT were requested. Alternatively, one 250µl EDTA specimen for POC testing and one dried blood spot card, with at least three 70µl spots, for CLT were requested. Specimens were collected by doctors and nurses as part of their routine duties.POC EID testing was conducted using either the Xpert™ HIV-1 Qual or the m-PIMA HIV-1/2 Detect assays
Comparative	
Notes	
Methodological quality	

Kufa 2020b *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		Unclear risk	

Meggi 2017

Study characteristics			
Patient Sampling	Infants excluded from the study were those older than 24 hours of age, those not born at the participating health facilities, and those with serious medical conditions, delivery complications, born through Caesarean section, or born to mothers with mental illness. The cohort of infants tested at birth was followed up and tested again with both laboratory and POC assays for the routine EID screen at 4 ± 6 weeks.		
Patient characteristics and setting	HIV-exposed infants at birth; primary healthcare maternity wards in Mozambique. The cohort of infants tested at birth was followed up and tested again with both laboratory and POC assays for the routine EID screen at 4 ± 6 weeks.		
Index tests	Alere q HIV-1/2 Detect system (Alere Inc, Waltham, MA, USA); fresh whole blood capillary heel/toe prick		
Target condition and reference standard(s)	HIV-1; Roche CAP/CTM 96 HIV-1 qualitative test v2 (Roche Molecular Diagnostics, Branchburg, NJ, USA)		
Flow and timing	HIV-exposed infants were tested at maternity wards by trained nurses using the Alere q HIV-1/2 Detect system (Alere Inc, Waltham, MA, USA) within 24 hours of birth. Dried blood spot specimens (Whatman 903, GE Healthcare Biosciences, Pittsburgh, PA, USA) were simultaneously drawn from heel or toe pricks, and transferred within 1 week for blinded testing at central reference laboratories.		
Comparative			
Notes	Laboratory and POC birth test results were not used for patient diagnosis, as they were not part of routine care.		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Meggi 2017 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		Low risk	

Ondiek 2017a

Study characteristics	
Patient Sampling	Unclear; laboratory evaluation; in the case of Kenyan infants, by heel or finger pricks
Patient characteristics and setting	Kenya; laboratory setting
Index tests	Simple AMplification-Based Assay (SAMBA) HIV-1 Qual Whole Blood Test; fresh whole blood via heel/finger prick
Target condition and reference standard(s)	HIV-1 proviral DNA and RNA; Roche COBAS AmpliPrep/COBAS TaqMan (CAP/CTM) HIV-1 assay
Flow and timing	Whole blood was collected in the case of Kenyan infants, by heel or finger pricks. Whole blood samples (150 mL) were tested within 24 hours of collection both with the SAMBA HIV-1 Qual Whole Blood Test (Diagnostics for the Real World) and with the Roche COBAS AmpliPrep/COBAS TaqMan (CAP/CTM) HIV-1 Qualitative test as performed by local trained technicians
Comparative	

Ondiek 2017a *(Continued)*

Notes			

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Ondiek 2017b

Study characteristics			
Patient Sampling	Unclear; laboratory setting; whole blood was collected by venepuncture into BD Vacutainer K2-EDTA tubes (Becton Dickinson, Franklin Lakes, NJ, USA)		
Patient characteristics and setting	HIV-exposed and -infected infants ≤ 12 months; Mulago Core Laboratory, Uganda		
Index tests	Simple AMplification-Based Assay (SAMBA) HIV-1 Qual Whole Blood Test; laboratory evaluation; fresh whole sample venepuncture		
Target condition and reference standard(s)	HIV-1 proviral DNA and RNA; Roche COBAS AmpliPrep/COBAS TaqMan (CAP/CTM) HIV-1 assay		
Flow and timing	In Kampala, Uganda, whole blood and DBS specimens were collected between January and September 2014 from a total of 311 infants, including 201 vertically exposed infants. Whole blood samples were tested with the SAMBA assay at the Mulago Core Laboratory by local trained technicians within 1–2 hours of collection. DBS samples were sent to Central Public Health Laboratory within 3 days of preparation for testing with the CAP/CTM assay		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Ondiek 2017b *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Ondiek 2017c

Study characteristics	
Patient Sampling	Unclear; laboratory evaluation; whole blood was collected either by venepuncture into BD Vacutainer K2-EDTA tubes (Becton Dickinson, Franklin Lakes, NJ, USA) or, in the case of Kenyan infants, by heel or finger pricks
Patient characteristics and setting	HIV-exposed and -infected infants ≤ 18 months; National Microbiology Reference Laboratory, Zimbabwe
Index tests	Simple AMplification-Based Assay (SAMBA) HIV-1 Qual Whole Blood Test; laboratory setting; fresh whole blood samples via venepuncture
Target condition and reference standard(s)	HIV-1 proviral DNA and RNA; Roche COBAS AmpliPrep/COBAS TaqMan (CAP/CTM) HIV-1 assay
Flow and timing	DBS samples were collected from 99 exposed infants recruited from Harare Central Hospital between July and August 2014. Whole blood and DBS samples were tested within 6 hours of collection with the SAMBA and CAP/CTM assays, respectively, as per-

Ondiek 2017c *(Continued)*

	formed by local trained technicians at the National Microbiology Reference Laboratory (NMRL).
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		

Ondiek 2017c *(Continued)*

Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Opollo 2018

Study characteristics	
Patient Sampling	This study was conducted amongst mother/guardian-infant pairs attending expanded programmes of immunization (EPI) services at selected clinics and maternity at Ndhiwa sub-county hospital. Eligible infants attending EPI were those aged 6 weeks (+/- 4 weeks) and 9 months (+/- 1 month) and all infants born in the maternity hospital. Mother-baby pairs were excluded mainly because of the age of infants, did not consent, or were disabled. Samples were collected from HIV-exposed children attending the health facilities at all these service points.
Patient characteristics and setting	HIV-exposed children < 18 months of age; field setting in Western Kenya (selected clinics and maternity at Ndiwa)
Index tests	Cepheid GeneXpert HIV-1 Qual (GeneXpert) technology; fresh whole blood on Dried Blood Spot (DBS) via finger/heel prick
Target condition and reference standard(s)	HIV-1 infection; Roche CAP/CTM HIV-1 qualitative PCR
Flow and timing	The filter paper was air-dried at the health facilities and transported daily to laboratory hubs where the POC GeneXpert devices were placed, and for temporary storage in preparation for transport to the KEMRI HIV research laboratory in Kisumu, where routine EID was conducted.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern

Opollo 2018 *(Continued)*

DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Sabi 2019

Study characteristics	
Patient Sampling	This study included HIV-infected pregnant women above 18 years of age and, after delivery, their newborn babies. All recruited women provided written informed consent for themselves and their babies after receiving verbal and written study information. Informed consent was not obtained in a state of full labour or when participants were experiencing birth-related stress, pain, or emotional distress. Women and infants were excluded from study participation if immediate maternal or infant medical assistance was required; in the case of a stillbirth or severe congenital malformation; if the birth was > 48 hours prior to enrolment; or if the participant was unlikely to comply with the protocol, as judged by the investigator.
Patient characteristics and setting	HIV-exposed infants at birth and at postpartum weeks 1, 2, 3, and 6; obstetric health facilities in Tanzania

Sabi 2019 *(Continued)*

Index tests	Xpert HIV-1 Qual assay on the GeneXpert system (Cepheid, Sunnyvale, CA, USA) at health facility; fresh whole blood sample via heel prick
Target condition and reference standard(s)	HIV-1; COBAS TaqMan V2 (Roche Molecular Systems, Branchburg, NJ, USA)
Flow and timing	At each testing point, DBS samples were collected for qualitative HIV-DNA confirmation using the COBAS TaqMan V2 (Roche Molecular Systems, Branchburg, NJ, USA); the confirmation tests were performed at week 6 for all infants, according to the routine Tanzanian infant HIV testing algorithm, and immediately for all infants with positive Xpert POC results. Retrospective Xpert HIV-1 Qual testing was performed from stored DBS (Xpert DBS) for all HIV-infected infants at each time point, as well as in a subset of non-infected infants for comparison of the Xpert DBS and the Xpert POC.
Comparative	
Notes	Only positive Xpert POCs and a subset of negative Xpert POCs were confirmed immediately; others were confirmed later.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Sabi 2019 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		Unclear risk	

Spooner 2019

Study characteristics	
Patient Sampling	The study population consisted of HIV-exposed infants presenting for HIV-PCR testing at birth at Addington Hospital (a regional hospital in the city centre) and follow-up testing at a referral primary health centre clinic, Lancers Road Clinic (in the transport hub of Warwick triangle taxi rank). All infants of HIV-positive mothers were eligible if their mother consented to participate in the study.
Patient characteristics and setting	HIV-exposed infants presenting for HIV-PCR testing at birth and follow-up testing; hospital and clinic in Durban, South Africa
Index tests	Alere q HIV-1/2 Detect POC test; fresh whole blood sample drawn via heel prick
Target condition and reference standard(s)	HIV-1; COBAS AmpliPrep/COBAS Taq-Man (CAP/CTM) HIV-1 qualitative test v2.0 (Roche Molecular Systems Inc, Branchburg, NJ, USA)
Flow and timing	The POC instrument was placed in the well-baby examination room at the PHC clinic and, as mothers and babies presented for their clinic visit, they were pre-test counselled, they consented, and the PCR testing was performed. The implementation of the Alere q HIV-1/2 Detect POC RNA PCR test was performed for HIV-exposed infants concurrently with the Standard of Care central laboratory DBS test. Results were given for both tests. Invalid reference test results (n = 3 retested at 1 week (1), 6 weeks (1), and time unclear (1) and included in the analysis)
Comparative	

Spooner 2019 *(Continued)*

Notes			

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Technau 2019

Study characteristics			
Patient Sampling	From 1 October 2014 through 30 April 2016, all identified HIV-positive women were invited to enrol their neonates in an observational cohort study of routine universal birth testing including this field evaluation of point-of-care testing. Laboratory-based testing was not dependent upon enrolment in the study.		
Patient characteristics and setting	HIV-exposed neonates at birth; maternity hospital in Johannesburg, South Africa; small satellite research laboratory on site		
Index tests	Cepheid Xpert HIV-1 qualitative assay (Cepheid, Sunnyvale, CA, USA); fresh whole blood via venepuncture		
Target condition and reference standard(s)	HIV-1; Roche COBAS TaqMan HIV-1 qualitative test version 2.0 (Roche Molecular Systems Inc, Branchburg, NJ, USA)		
Flow and timing	Neonatal whole blood was sampled by venepuncture in the postnatal ward or during neonatal admission. Cord blood was never sampled. The LABT sample was collected into a 0.5-millilitre ethylenediaminetetra-acetic acid (EDTA) tube and sent to the national laboratory for HIV PCR testing (Roche COBAS TaqMan HIV-1 qualitative test version 2.0, Roche Molecular Systems Inc, Branchburg, NJ, USA), where processing was done by routine, non-study staff. From the same blood draw, an additional identical 0.5-millilitre whole blood sample was collected for POCT (Cepheid Xpert HIV-1 qualitative assay, Cepheid, Sunnyvale, CA, USA) for processing by study staff in a small satellite research laboratory on site. All mothers received an appointment to collect their neonate's LABT result within 1 week.		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			

Technau 2019 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		Low risk	

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdulrahaman 2008	Ineligible study type: feasibility or effectiveness study
Achwoka 2018	Ineligible study type: feasibility or effectiveness study
Agutu 2019	Ineligible study type: review
Ahmed 2013	Ineligible study type: review
Alvarez 2017	Ineligible index test: not POC NAT
Anaba 2019	Ineligible index test: not POC NAT
Anoje 2012	Ineligible index test: not POC NAT

Study	Reason for exclusion
Audu 2015	Ineligible index test: not POC NAT
Aulicino 2006	Ineligible index test: not POC NAT
Avettand-Fènoël 2009	Ineligible index test: not POC NAT
Babatunde 2019	Ineligible index test: not POC NAT
Beavers 2009	Ineligible index test: not POC NAT
Beyene 2017	Conference abstract
Bianchi 2019	Ineligible study type: feasibility or effectiveness study
Bisschoff 2019	Ineligible study type: feasibility or effectiveness study
Braun 2011	Ineligible study type: feasibility or effectiveness study
Bredberg-Rådén 1995	Ineligible index test: not POC NAT
Buchanan 2012	Ineligible index test: not POC NAT
Burgard 2012	Ineligible index test: not POC NAT
Burton 2015	Conference abstract
Cañizal 2010	Ineligible index test: not POC NAT
Chang 2014	Ineligible index test: not POC NAT
Chang 2015	Ineligible index test: not POC NAT
Chang 2017	Ineligible population: adults
D'Angelo 2007	Ineligible index test: not POC NAT
Dunning 2015a	Ineligible study type: review
Dunning 2017b	Ineligible index test: not POC NAT
Dunning 2017c	Ineligible study type: cost-effectiveness analysis
Horwood 2012	Ineligible index test: not POC NAT
Ibrahim 2017a	Ineligible study type: 2-gate study with negative controls
Ibrahim 2017b	Duplicate
ISRCTN38911104	Protocol
Jani 2017	Conference abstract
Jani 2018a	Ineligible study type: feasibility or effectiveness study
Jani 2018b	Duplicate

Study	Reason for exclusion
Jani 2019	Ineligible study type: review
Kébé 2011	Ineligible index test: not POC NAT
Lambert 2003	Ineligible index test: not POC NAT
Lee 2012	Ineligible index test: not POC NAT
Lyamuya 1996	Ineligible index test: not POC NAT
Madaline 2017	Ineligible index test: not POC NAT
Maliwichi 2014	Ineligible index test: not POC NAT
Maritz 2014	Conference abstract
Martin 2017	Ineligible index test: not POC NAT
Mashamba-Thompson 2018	Ineligible study type: feasibility or effectiveness study
Mazanderani 2016	Ineligible index test: not POC NAT
Mazanderani 2018	Ineligible index test: not POC NAT
McCann 2020	Ineligible study design: cost-effectiveness analysis
McCollum 2014	Ineligible index test: not POC NAT
McFall 2015	Ineligible index test: not POC NAT (FINA method for the sensitive detection of proviral HIV DNA)
Molina 2004	Ineligible index test: not POC NAT
Moyo 2020	Ineligible study type: feasibility or effectiveness study
Murray 2017	Ineligible study type: 2-gate study with negative controls
Mwashiuya 2018	Conference abstract
Mwenda 2018	Ineligible study type: feasibility or effectiveness study
NCT02545296	Protocol
NCT02634450	Protocol
NCT03133728	Protocol
NCT03435887	Protocol
NCT03824067a	Protocol
NCT03824067b	Duplicate
NCT04032522a	Protocol
NCT04032522b	Protocol

Study	Reason for exclusion
NCT04206878	Protocol
Ndlovu 2018	Ineligible study type: feasibility or effectiveness study
Ndondoki 2013	Ineligible index test: not POC NAT
Newbould 2010	Conference abstract
Nyangwa 2020	Ineligible population: inclusion criteria (0 to 14 years)
Olupot-Olupot 2017	Conference abstract
Phiri 2017	Ineligible index test: not POC NAT
Reisler 2001	Ineligible index test: not POC NAT
Ritchie 2016	Ineligible study type: analytical accuracy study
Rouet 2001	Ineligible index test: not POC NAT
Rubio-Garrido 2019	Ineligible reference test
Sabi 2018	Duplicate
Sandbulte 2019	Protocol
Sherman 2012	Ineligible index test: not POC NAT
Sivapalasingam 2007	Ineligible index test: not POC NAT
Sivapalasingam 2012	Ineligible index test: not POC NAT
Tchendou 2019	Ineligible study type: analytical accuracy study
Tembo 2019	Conference abstract
Vubil 2020	Ineligible index test: not POC NAT
Wexler 2019	Ineligible study type: qualitative study
Young 2000	Ineligible index test: not POC NAT
Zhang 2013	Ineligible index test: not POC NAT

FINA: filtration isolation of nucleic acids
POC NAT: point-of-care nucleic acid-based testing

DATA

Presented below are all the data for all of the tests entered into the review.

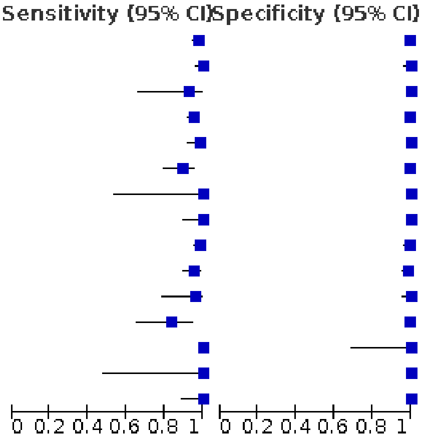
Table Tests. Data tables by test

Test	No. of studies	No. of participants
1 POC NAT early infant diagnosis	15	15120

Test 1. POC NAT early infant diagnosis

POC NAT early infant diagnosis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bwana 2019	258	2	7	634	0.97 [0.95, 0.99]	1.00 [0.99, 1.00]
Ceffa 2016	92	0	0	104	1.00 [0.96, 1.00]	1.00 [0.97, 1.00]
Dunning 2017a	13	0	1	380	0.93 [0.66, 1.00]	1.00 [0.99, 1.00]
Hsiao 2016	192	2	9	832	0.96 [0.92, 0.98]	1.00 [0.99, 1.00]
Jani 2014	64	1	1	761	0.98 [0.92, 1.00]	1.00 [0.99, 1.00]
Kufa 2020a	60	18	7	4163	0.90 [0.80, 0.96]	1.00 [0.99, 1.00]
Kufa 2020b	6	0	0	820	1.00 [0.54, 1.00]	1.00 [1.00, 1.00]
Meggi 2017	33	0	0	1827	1.00 [0.89, 1.00]	1.00 [1.00, 1.00]
Ondiek 2017a	200	1	3	131	0.99 [0.96, 1.00]	0.99 [0.96, 1.00]
Ondiek 2017b	100	3	5	203	0.95 [0.89, 0.98]	0.99 [0.96, 1.00]
Ondiek 2017c	23	0	1	75	0.96 [0.79, 1.00]	1.00 [0.95, 1.00]
Opollo 2018	25	2	5	889	0.83 [0.65, 0.94]	1.00 [0.99, 1.00]
Sabi 2019	588	0	0	10	1.00 [0.99, 1.00]	1.00 [0.69, 1.00]
Spooner 2019	5	0	0	435	1.00 [0.48, 1.00]	1.00 [0.99, 1.00]
Technau 2019	30	2	0	2097	1.00 [0.88, 1.00]	1.00 [1.00, 1.00]



ADDITIONAL TABLES

Table 1. Indirect test comparisons

Tests compared	Difference sensitivity % (95% CI[a] for difference, P value for difference) (Indirect comparison)
Xpert sens minus Alere sens	2.6 (−0.3 to 5.5, P = 0.08)
Xpert sens minus SAMBA sens	2.0 (−0.1 to 4.9, P = 0.195)
SAMBA sens minus Alere sens	0.7 (−2.1 to 3.5, P = 0.651)

[a]95% CI: 95% confidence interval

Table 2. Variation in sensitivity and specificity of point-of-care nucleic acid-based testing

		Sensitivity (95% CI)[a]	Specificity (95% CI)[a]
Main meta-analysis[b]	n = 15	98.6% (96.1 to 99.5)	99.9% (99.7 to 99.9)
Subgroup analyses[c]			
Age	Birth (n = 6)[d]	99.0% (98.0 to 100)[e]	99.8% (99.7 to 99.9)[e]

Table 2. Variation in sensitivity and specificity of point-of-care nucleic acid-based testing *(Continued)*

	≤ 12 months (n = 3)	96.6% (94.3 to 98.0)	99.6% (99.0 to 99.9)[e]
	≤ 18 months (n = 5)	97.9% (91.9 to 99.5)	99.8% (99.5 to 99.9)[e]
Test type	Xpert (n = 6)	99.2% (88.1 to 100.0)	99.7% (99.5 to 99.8)[e]
	Alere (n = 6)	96.6% (94.0 to 98.1)	99.9% (99.8 to 100.0)[e]
	SAMBA (n = 3)	97.3% (94.4 to 98.7)	99.0% (97.5 to 99.7)[e]
Location	Lab (n = 5)	97.4% (94.8 to 98.7)	99.6% (99.0 to 99.8)[e]
	Field (n = 10)	98.7% (93.4 to 99.8)	99.8% (99.7 to 99.9)[e]
Sample type	Dried blood samples (n = 4)	97.7% (89.4 to 99.5)	99.8% (99.5 to 99.9)[e]
	Whole blood fresh samples (n = 11)	98.4% (94.9 to 99.5)	99.8% (99.7 to 99.8)[e]
Sensitivity analyses[f]			
Risk of bias	Excluding high risk of bias (n = 14)	98.4% (95.6 to 99.4)	99.8 (99.7 to 99.9)
Influential studies	Excluding Opollo 2018 (n = 14)	98.9% (96.7 to 99.6)	99.9% (99.7 to 99.9)
	Excluding Hsiao 2016 (n = 14)	98.6% (97.7 to 99.2)	99.9% (99.8 to 99.9)

[a]95% CI: 95% confidence interval
[b]Main meta-analysis: we fitted the bivariate model with random-effects, which accounts for within-study variability and correlation of sensitivity and specificity.
[c]Subgroup analyses: with fewer studies, the bivariate model did not converge. As specificity is 100% for all, except for two studies where it is 99%, all analyses are meta-analyses of sensitivity.
[d]At birth, all studies have 100% sensitivity and 100% specificity (no pooling).
[e]Where we could not do a meta-analysis, we combined the fractions across the studies and computed the proportion and its CI using the binomial exact method.
[f]Sensitivity analyses: we fitted the bivariate model with random-effects, which accounts for within-study variability and correlation of sensitivity and specificity, and restricted the analyses as shown above.

APPENDICES

Appendix 1. Search sources and strategies

The following strategies are based on the most recent updated search we conducted on 1 and 2 February 2021

Medline (Ovid) Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <2019 to February 1, 2021>

Search date: 1 Feb 2021

Search Strategy:--

1 exp HIV/ or exp HIV Infections/ or Acquired Immunodeficiency Syndrome/

2 (Acquired Immunodeficiency Syndrome* or Acquired Immunologic Deficiency Syndrome* or Acquired Immun* Deficiency Syndrome*).ab. or (Acquired Immunodeficiency Syndrome* or Acquired Immunologic Deficiency Syndrome* or Acquired Immun* Deficiency Syndrome*).ti.

3 (Human Immunodeficiency Virus* or Human T Cell Lymphotropic Virus* or Human T Lymphotropic Virus* or Human T Cell Leukemia Virus* or LAV HTLV III or Lymphadenopathy Associated Virus*).ab. or (Human Immunodeficiency Virus* or Human T Cell Lymphotropic Virus* or Human T Lymphotropic Virus* or Human T Cell Leukemia Virus* or LAV HTLV III or Lymphadenopathy Associated Virus*).ti.

4 (HIV or HIV 1 or HIV 2 or HIV AIDS or HIV I or LAV 2 or LAV HTLV III or HIV II or HTLV III or HTLV IV or SBL 6669 or AIDS).ab. or (HIV or HIV 1 or HIV 2 or HIV AIDS or HIV I or LAV 2 or LAV HTLV III or HIV II or HTLV III or HTLV IV or SBL 6669 or AIDS).ti.

5 1 or 2 or 3 or 4

6 exp infant/ or exp infant, newborn/ or exp child/

7 (infant? or newborn? or neonat$ or newly born? or perinatal or peri natal or postnatal or post natal or postpartum? or puerperium? or peripartum? or toddler$ or child$ or preschool$ or pre-school$ or pediatric$ or paediatric$ or baby or babies).ab. or (infant? or newborn? or neonat$ or newly born? or perinatal or peri natal or postnatal or post natal or postpartum? or puerperium? or peripartum? or toddler$ or child$ or preschool$ or pre-school$ or pediatric$ or paediatric$ or baby or babies).ti.

8 6 or 7

9 5 and 8

10 Early Diagnosis/ and Point-of-Care Systems/

11 ((Early diagnos$ or early detect$ or Early Infant$ Diagnos$ or EID) and (Point of Care or Care Technolog$ Point$ or Bedside Test$ or Bedside Comput$ or Bedside Technolog$ or Rapid Test$ or Rapid Diagnos$ or RDT)).ti,ab.

12 10 or 11

13 9 and 12

Embase (Ovid)

Search date: 1 February 2021

Database: Embase 2019-Present, updated daily

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14 exp Human immunodeficiency virus/ or exp acquired immune deficiency syndrome/ or exp human immunodeficiency virus infection/ or exp human immunodeficiency virus 1/ or exp human immunodeficiency virus 2/

15 (Acquired Immunodeficiency Syndrome? or Acquired Immunologic Deficiency Syndrome? or Acquired Immun? Deficiency Syndrome? or Human Immunodeficiency Virus$ or Human T Cell Lymphotropic Virus$ or Human T Lymphotropic Virus$ or Human T Cell Leukemia Virus$ or LAV HTLV III or Lymphadenopathy Associated Virus$).ab. or (Acquired Immunodeficiency Syndrome? or Acquired Immunologic Deficiency Syndrome? or Acquired Immun? Deficiency Syndrome? or Human Immunodeficiency Virus$ or Human T Cell Lymphotropic Virus$ or Human T Lymphotropic Virus$ or Human T Cell Leukemia Virus$ or LAV HTLV III or Lymphadenopathy Associated Virus$).ti.

16 (HIV or HIV 1 or HIV 2 or HIV AIDS or HIV I or LAV 2 or LAV HTLV III or HIV II or HTLV III or HTLV IV or SBL 6669 or AIDS).ab. or (HIV or HIV 1 or HIV 2 or HIV AIDS or HIV I or LAV 2 or LAV HTLV III or HIV II or HTLV III or HTLV IV or SBL 6669 or AIDS).ti.

17 14 or 15 or 16

18 exp infant/ or exp newborn/ or exp children/

19 (infant? or newborn? or neonat$ or newly born? or perinatal or peri natal or postnatal or post natal or postpartum? or puerperium? or peripartum? or toddler$ or child$ or preschool$ or pre-school$ or pediatric$ or paediatric$ or baby or babies).ab. or (infant? or newborn? or neonat$ or newly born? or perinatal or peri natal or postnatal or post natal or postpartum? or puerperium? or peripartum? or toddler$ or child$ or preschool$ or pre-school$ or pediatric$ or paediatric$ or baby or babies).ti.

20 18 or 19

21 17 and 20

22 (Early Diagnosis/ and point of care testing/) or exp rapid test/

23 ((Early diagnos$ or early detect$ or Early Infant$ Diagnos$ or EID) and (Point of Care or Care Technolog$ Point$ or Bedside Test$ or Bedside Comput$ or Bedside Technolog$ or Rapid Test$ or Rapid Diagnos$ or RDT)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

24 22 or 23

25 21 and 24

26 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/

27 human/ or normal human/ or human cell/

28 26 and 27

29 26 not 28

30 25 not 29

31 limit 30 to yr="2019 -Current"

32 limit 31 to exclude medline journals

World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)

http://apps.who.int/trialsearch/

Date: 2 February 2021

HIV OR human immunodeficiency virus in the Condition

AND

early diagnosis OR early detection OR point of care OR bedside test OR Rapid test in the Intervention

Recruitment status: ALL

Date of registration is between 01/01/2020 and 02/02/2021

ClinicalTrials.gov

www.clinicaltrials.gov/

Date of search: 2 February 2021

Condition or disease: (Acquired Immunodeficiency Syndrome* OR Acquired Immunologic Deficiency Syndrome* OR Acquired Immun* Deficiency Syndrome* OR Human Immunodeficiency Virus* OR AIDS* OR HIV*)

Other terms: (Early diagnos* OR early detect* OR Early Infant* Diagnos* OR EID OR Point of Care OR Care Technolog* Point* OR Bedside Test* OR Bedside Comput* OR Bedside Technolog* OR Rapid Test* or Rapid Diagnos* or RDT)

All studies

First Posted: From 01/01/2020 To 02/02/2021

Web of Science Core Collection

Includes: Science Citation Index Expanded (SCI-EXPANDED)/ and Conference Proceedings Citation Index- Science (CPCI-S).

Date of search: 2 February 2021

TITLE: ((Acquired Immunodeficiency Syndrome*ORAcquired ImmunologicDeficiency Syndrome*ORAcquired Immun*Deficiency Syndrome* OR Human Immunodeficiency Virus* OR Human T Cell Lymphotropic Virus* OR Human T Lymphotropic Virus* OR Human T Cell Leukemia Virus* OR LAV HTLV III OR Lymphadenopathy Associated Virus* OR HIV OR HIV 1 OR HIV 2 OR HIV/AIDS OR HIV I OR LAV 2 OR LAV HTLV III OR HIV II OR HTLV III OR HTLV IV OR SBL 6669 OR AIDS))

AND

TITLE: ((infant* OR newborn* OR neonat* OR newly born* OR perinatal OR peri natal OR postnatal OR post natal OR postpartum* OR puerperium* OR peripartum* OR toddler* OR child* OR preschool* OR pre-school* OR pediatric* OR paediatric* OR baby OR babies))

AND

TITLE: ((Early diagnos* OR early detect* OR Early Infant* Diagnos* OR EID OR Point of Care OR Care Technolog* Point* OR Bedside Test* OR Bedside Comput* OR Bedside Technolog* OR Rapid Test* OR Rapid Diagnos* OR RDT))

Timespan: 2020-2021. **Indexes:** SCI-EXPANDED, CPCI-S.

LILACS (Virtual Health Library)

Date of search: 2 February 2021

Words: (Acquired Immunodeficiency Syndrome$ OR Acquired Immunologic Deficiency Syndrome$ OR Acquired Immun$ Deficiency Syndrome$ OR Human Immunodeficiency Virus$ OR Human T Cell Lymphotropic Virus$ OR Human T Lymphotropic Virus$ OR Human T Cell Leukemia Virus$ OR LAV HTLV III OR Lymphadenopathy Associated Virus$ OR HIV OR HIV 1 OR HIV 2 OR HIV/AIDS OR HIV I OR LAV 2 OR LAV HTLV III OR HIV II OR HTLV III OR HTLV IV OR SBL 6669 OR AIDS) AND

Words: (infant$ OR newborn$ OR neonat$ OR newly born$ OR perinatal OR peri natal OR postnatal OR post natal OR postpartum$ OR puerperium$ OR peripartum$ OR toddler$ OR child$ OR preschool$ OR pre-school$ OR pediatric$ OR paediatric$ OR baby OR babies) AND

Words: (Early diagnos$ OR early detect$ OR Early Infant$ Diagnos$ OR EID OR Point of Care OR Care Technolog$ Point$ OR Bedside Test$ OR Bedside Comput$ OR Bedside Technolog$ OR Rapid Test$ OR Rapid Diagnos$ OR RDT)

CENTRAL in Cochrane Library

Date of search: 2 February 2021

#1 MeSH descriptor: [HIV] explode all trees

#2 MeSH descriptor: [HIV Infections] explode all trees

#3 Acquired Immunodeficiency Syndrome*

#4 Acquired Immunologic Deficiency Syndrome*

#5 Acquired Immun* Deficiency Syndrome*

#6 Human Immunodeficiency Virus*

#7 Human T Cell Lymphotropic Virus*

#8 Human T Lymphotropic Virus*

#9 Human T Cell Leukemia Virus*

#10 LAV HTLV III

#11 Lymphadenopathy Associated Virus*

#12 HIV

#13 “HIV 1”

#14 “HIV 2”

#15 “HIVAIDS”

#16 HIV I

#17 “LAV 2”

#18 LAV HTLV III

#19 HIV II

#20 HTLV III

#21 HTLV IV

#22 “SBL 6669”

#23 AIDS

#24 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23

#25 MeSH descriptor: [Infant] explode all trees

#26 MeSH descriptor: [Infant, Newborn] explode all trees

#27 MeSH descriptor: [Child] explode all trees

#28 infant*

#29 newborn*

#30 neonat*

#31 newly born*

#32 perinatal

#33 peri natal

#34 postnatal

#35 post natal

#36 postpartum*

#37 puerperium*

#38 peripartum*

#39 toddler*

#40 child*

#41 preschool*

#42 pre-school

#43 pediatric*

#44 paediatric*

#45 baby

#46 babies

#47 #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46

#48 MeSH descriptor: [Early Diagnosis] explode all trees

#49 Early diagnos*

#50 early detect*

#51 early infant* diagnos*

#52 EID

#53 #48 OR #49 OR #50 OR #51 OR #52

#54 MeSH descriptor: [Point-of-Care Systems] explode all trees

#55 Point of Care or Care Technolog* Point* or Bedside Test* or Bedside Comput* or Bedside Technolog* or Rapid Test* or Rapid Diagnos* or RDT

#56 #54 OR #55

#58 #24 AND #47 AND #53 AND #56 with Cochrane Library publication date from Jan 2020 to present, in Trials

WHO Global Index Medicus

Search date: 2 February 2021

https://www.globalindexmedicus.net/

Searched in Title, Abstract, Subject:

(tw:((acquired immunodeficiency syndrome*) OR (acquired immunologic deficiency syndrome*) OR (acquired immun* deficiency syndrome*) OR (human immunodeficiency virus*) OR (hiv) OR (hiv/aids) OR (aids))) AND (tw:((early diagnos*) OR (early detect*) OR (early infant* diagnos*) OR (eid) OR (point of care) OR (care technolog* point*) OR (bedside test*) OR (bedside comput*) OR (bedside technolog*) OR (rapid test*) OR (rapid diagnos*) OR (rdt))) AND (tw:((infant*) OR (newborn*) OR (neonat*) OR (newly born*) OR (perinatal) OR (peri natal) OR (postnatal) OR (post natal) OR (postpartum*) OR (puerperium*) OR (peripartum*) OR (toddler*) OR (child*) OR (preschool*) OR (pre-school*) OR (pediatric*) OR (paediatric*) OR (baby) OR (babies)))

Appendix 2. Data extraction

We will extract the following information for cross-sectional, cohort, and case-control studies.

Study ID: we will identify studies by the name of the first author and the year in which the study was first published.

Eligibility: study design, population (infants and children aged ≤ 18 months), HIV status.

Study details: aim/objective of the study, inclusion and exclusion criteria, study design, prospective/retrospective, whether study was restricted to a subgroup of a larger cohort, how sample size was determined, region and country, setting (inpatients, outpatients), study start and end dates.

Study population: description of the participants included in the study (age, gender), predefined inclusion or exclusion criteria (or both), special populations, number of participants recruited/included in the study, how participants were allocated to groups.

Tests: details of POC early infant diagnosis test and reference tests used in groups, manufacturer/assay name, regulatory status, sample used, test cut-off and performance, staff performing the tests, test conduct, test failure rates.

Outcomes: true-positives, false-positives, false-negatives, true-negatives.

Appendix 3. QUADAS-2 details

Domain	Participant selection	Index test (IT)	Reference standard (RS)	Flow and timing
Description	**Methods of participant selection**	**How IT was conducted and reported**	**How RS was conducted and reported**	**Describe participants who did not receive and time interval between IT or RS**
Signalling questions (yes, no, unclear)	Consecutive or random sample of participants? Yes if study reported consecutive or random sampling of participants. No if study reported other types of sam-	IT results interpreted without knowledge of the results of RS? Yes if it was clear that the IT results were interpreted without knowledge of RS results. No if it was apparent that the IT results were interpreted with knowledge of the RS results.	RS likely to correctly classify the target condition? Yes if laboratory reference test was used at clearly stated threshold (manufacturer recommended threshold). No if laboratory reference test used with data-driven or post hoc threshold.	Appropriate interval between IT and RS? Yes if samples for both the IT and RS were drawn at the same time or within an interval of 24 hours.

(Continued)

	pling, e.g. convenience sampling or sampled based on results of prior tests. Unclear if there was insufficient detail to judge.	Unclear if there was insufficient detail to judge.	Unclear if there was insufficient detail to judge.	No if samples for the IT and RS were drawn at an interval of more than 1 week. Unclear if there was insufficient detail to judge.
	Was a case-control design with healthy controls avoided? Yes if the case-control design above was not used. No if the case-control design above was used. Unclear if there was insufficient detail about study design. Did the study avoid inappropriate exclusions? Yes No Unclear	Prespecified threshold used? Yes if threshold as per manufacturer's instructions was reported. Test results reported as positive or negative. No if threshold as per manufacturer's instructions was not used. Unclear if there was insufficient detail to judge.	RS results interpreted without knowledge of the results of IT? Yes if it was apparent that RS results were interpreted without knowing IT results. No if it was clear that RS results were interpreted whilst knowing IT results. Unclear if there was insufficient detail to judge.	Number of participants receiving RS/ same RS, and included in the analysis? Yes if all participants received an RS or the same RS regardless of IT results. No if only some participants received an RS or if different RS were used. Unclear if there was insufficient detail to judge.
Risk of bias (high, low, unclear)	Could the selection of participants have introduced bias?	Could the conduct or interpretation of the IT have introduced bias?	Could the RS, its conduct, or its interpretation have introduced bias?	Could the participant flow have introduced bias?
Applicability concerns (high, low, unclear)	Were there concerns that the included participants did not match the review question? High Low Unclear	Were there concerns that the IT, its conduct, or its interpretation differed from the review question? High if the IT was a prototype, not commercially available, or conducted in a nearby laboratory. Low if the IT was commercially available or conducted in a field setting. Unclear if there was insufficient information to permit a judgement.	Were there concerns that the target condition as defined by the RS did not match the review question? High if the IT was not commercially available. Low if the IT was commercially available. Unclear if there was insufficient information to permit a judgement.	-

Scoring criteria for risk of bias

- If all signalling questions for a domain are answered 'yes', then we will judge the risk of bias to be 'low'.
- If any signalling question is answered 'no', this will flag the potential for bias, and we will judge risk of bias with a senior review author.

(Continued)

- If all or most signalling questions are answered 'no', then we will judge the risk of bias as 'high'.
- We will assign the 'unclear' category when the study authors report insufficient data to permit a judgement.

HISTORY

Protocol first published: Issue 11, 2018

CONTRIBUTIONS OF AUTHORS

EO and FG were involved in study selection, data extraction, and quality and GRADE assessment.

EO and SM conducted the analyses.

All authors (EO, FG, SM, JD) contributed to the draft manuscript and its revisions.

Jon Deeks was unable to sign-off on the final review version, but co-authors agreed he fully contributed to the review.

DECLARATIONS OF INTEREST

We presented preliminary findings of this review to the WHO Guideline Meeting Group in Geneva, Switzerland in June 2015.

EO: no known conflicts of interest.

SM: received funding from the WHO to complete the initial review presented to the WHO Guideline Meeting Group in 2015.

FG: no known conflicts of interest.

JD: received funding from the WHO to complete the initial review and present it to the WHO Guideline Meeting Group in 2015.

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External sources

- Foreign, Commonwealth and Development Office (FCDO), UK

  Project number 300342-104
- World Health Organization, Switzerland

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- UK Medical Research Council/DFID, UK

  EO is supported by an MRC/DFID African Research Leader award. Project number T008768

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Investigation of heterogeneity

In the protocol, we stated that we would investigate the site of index test evaluation (near or true point-of-care (POC)) as a source of heterogeneity in test accuracy estimates (Ochodo 2018). In the review we modified the definition of site of index test evaluation as field (near or true POC) versus laboratory evaluation. Laboratory evaluations of POC tests were included, and we did not want to disregard this information. In practice, tests with POC platforms are also conducted in laboratory settings. We also included a study with a participant cut-off of ≤ 24 months, and checked its effect on the summary estimates through a sensitivity analysis. These were not stated a priori in the protocol.