Point of care circulating cathodic antigen accuracy in the diagnosis of schistosome infection: systematic review and meta-analysis

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ABSTRACT

Objective We assessed the diagnostic accuracy of POC-CCA test for schistosome infections using Kato-Katz technique (for *Schistosoma mansoni* and *S. japonicum*) or 10 mL urine filtration (for *S. haematobium*) as reference.

Methods We searched MEDLINE, EMBASE and LILACS to 30th September 2014, updated to 30th September 2015, as well as the Cochrane Library, reference lists and grey literature, and we contacted experts for unpublished studies. Twenty-seven published studies (1994-2014) met the inclusion criteria and were presented as sensitivity and specificity with 95 % CIs. Latent class bivariate modelling (LCBM) captured the between-study test variability.

Findings Single POC-CCA performed better than single Kato-Katz test (pooled sensitivity 0.90, 95% CI 0.84-0.94 and specificity 0.56, 95% CI 0.54-0.61; n=7) or three Kato-Katz tests (sensitivity 0.85, 95% CI 0.80-0.88 and specificity 0.66, 95% CI 0.54-0.76; n=14) for detecting *S. mansoni*. Accuracy from area under the ROC curve of single POC-CCA versus single Kato-Katz was 0.86. There is no demonstrable advantage of three over single CCA tests. LCBM identified two POC-CCA classes. Sensitivity analyses showed that the results were not strongly influenced by any particular study. Both CCA sensitivity and specificity appeared to be poor for *S. haematobium*. No studies were found for *S. japonicum*. POC-CCA performed better in high than low endemicity settings, and participants considered the urine-based POC-CCA acceptable, but data on comparative costs of applying POC-CCA and Kato-Katz is scarce.

Conclusion POC-CCA test may represent an effective tool for monitoring and evaluation of *S. mansoni* control programmes, but the evidence for other schistosome infections is inconclusive.

BACKGROUND

Schistosomiasis, caused by a group of flat worms that reside in the blood vessels in humans, is common among low income countries in the tropical and sub-tropical regions whose health systems face difficulties to provide basic care at the peripheral level.[1] An estimated 800 million people are at risk of the infection and over 207 million have the infection.[2-5] A person with schistosomiasis may be re-infected repeatedly even when regular treatment is provided[6-7], necessitating repeated screening and treatment in endemic populations. Five species, namely *Schistosoma mansoni*, *S. haematobium*, *S. japonicum*, *S. intercalatum* and *S. mekongi* can infect humans, but the three with significant public health impact are *S. mansoni* (common in Africa and some countries in South America), *S. haematobium* (endemic in Africa and the Middle East) and *S. japonicum* (mainly found in the People's Republic of China, Lao and the Philippines).[5] *S. mansoni* and *S. japonicum* cause intestinal schistosomiasis whilst *S. haematobium* causes urogenital schistosomiasis.

The WHO strategy for schistosomiasis control over the years has been active case detection and treatment with praziquantel (PZQ). Mass treatment with no prior diagnosis is usually employed in high endemicity settings.[5] For intestinal schistosomiasis, Kato-Katz thick smear[8] is the recommended diagnostic technique because of its assumed sensitivity, ability to classify intensity of infection, ease of use in the field and low cost whereas the standard 10 mL filtration of urine is used for urogenital schistosomiasis. Sensitivity of both the Kato-Katz and urine filtration depends on severity of the infection, and in low grade infections, sensitivity may be well below 30%.[9-10] For Kato-Katz test, for example, several stool specimens collected on different days are required to increase sensitivity.

Prevalence and intensity of infection have fallen significantly in most endemic areas following the introduction of mass drug administration (MDA) within the preventive chemotherapy (PC) strategy[5]. The routinely used diagnostic tests are no longer sensitive. Therefore, sensitive and easy-to-use at low cost diagnostic test is a necessity. Schistosomes release secretory metabolites identified as *Schistosoma*-genus specific circulatory antigens namely circulatory anodic antigen (CAA) and circulatory cathodic antigen (CCA)[11-13] linked with active infections[14] have been independently evaluated.[15-18]. Further research on CCA has produced the Point-Of-Care (POC) urine-based cassette assay[19] which has been validated in settings in Africa and that it is much more sensitive than the Kato-Katz test, even though it appears to suffer the same limitation when intensities of infection are low.[20-24]. Sensitivity of POC-CCA for urinary schistosomiasis has been variable in the few studies that have evaluated this.[19]

Given that systematic reviews are widely regarded as providing the best evidence to inform healthcare decisions[25-26], the WHO commissioned this review to assess the diagnostic accuracy of CCA test in a systematic review and meta-analysis to inform its control policy. Recently a Cochrane review has been published on this subject.[27]

This review was conducted with the primary objective to assess diagnostic accuracy of POC-CCA test for the diagnosis of schistosome infections using stool-based Kato-Katz thick smear (for *S. mansoni* and *S. japonicum*,) or standard 10 mL urine filtration (for *S. haematobium*) as reference standard. The secondary objectives were to assess the performance of ELISA for CCA in serum or urine, or other CCA assays and cost of field application of POC-CCA as well as effect of geographic location, age, endemicity and prior treatment on the performance of CCA. The study also compared time required for preparation and application; and user preference for POC-CCA versus Kato-Katz test and the standard 10 mL urine filtration method.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Eligibility standard forms based on predefined inclusion criteria were used to retrieve, select and assess quality of the studies.

Types of studies

Any study that compared CCA test with a reference standard (Kato-Katz or urine filtration, or both) for the diagnosis of schistosome infection; where precontrol infection status of the participants was not known; tests were performed in the same participants, and reported true-positives (TP, defined as individuals with infection who tested positive), true-negatives (TN, defined as those who did not have infection and tested negative), false-positives (FP, defined as individuals without infection who tested positive), and false-negatives (FN, defined as individuals with infection but tested negative) or where these could be extracted, were eligible for inclusion.

Types of participants

Individuals diagnosed microscopically for the presence of schistosome eggs in their stool (for *S. mansoni* and *S. japonicum*) using the Kato-Katz technique as reference standard[8] or in their urine using the standard 10 mL urine filtration method (for urogenital schistosomiasis).

Diagnostic thresholds

We used the commonly applied classification of intensity thresholds for Kato-Katz and the standard 10mL urine filtration tests based on WHO classification to define intensity of infection for interpreting our data. For Kato-Katz, this has been defined as "light infection" (< 100 EPG), "moderate infection" (100-399 EPG) and "heavy infection" (≥ 400 EPG) and for the standard 10 mL urine filtration test, "light infection" (≤ 50 eggs/10mL of urine) and "heavy infection" (> 50 eggs/10 mL of urine)". For POC-CCA we followed the manufacturer's definition classifying qualitatively as "trace as negative" (-), "trace as positive" (tr), "single positive" (+), "double positive" (++) and "triple positive" (+++).

REVIEW METHODS

Search methods for identification of studies

We searched MEDLINE, EMBASE and LILACS from inception to 30th September 2014, updated on 30th September 2015, using various search terms with no language restriction. We also searched BIOSIS, Web of Science, Google Scholar, Rapid Medical Diagnostics database, African Journals Online, Cochrane Infectious Diseases Group Specialized Register, CENTRAL (The Cochrane Library 2014 and updated in 2015) and mRCT. As accuracy studies present with lack of suitable methodological search filters, we maximised sensitivity of our search by using free texts based on the index test and target condition. We also hand-checked the reference lists of relevant articles and textbooks, and contacted experts for unpublished studies.

Selection of studies

One author searched the literature and retrieved studies using the aforementioned search strategy. Two authors screened the results to identify potentially relevant studies. Full study reports were obtained and assessed for eligibility for inclusion in the review using eligibility form based on the

predefined inclusion criteria. Twenty-seven studies published between 1994 and 2014 met the inclusion criteria. Any discrepancies were resolved through discussion between the authors.

Data extraction and management

Study characteristics such as citation, country and year study was conducted, study design and methods were recorded on standard forms. Information on diagnostic criteria of the index test and reference standard as well as number of urine samples tested and threshold classification was extracted. For Kato-Katz technique, data extracted included number of stool samples and slides, and volume of stool examined as well as how intensity of infection was classified (low, moderate and high). For urine specimens, information about number of urine specimens, and intensity categorization (low and high) were extracted. We extracted epidemiological and demographic data including endemicity status, region where the study was conducted, participants' prior treatment status, target population (preschool children, school-aged children, adults, whole population or representative sub-samples), sex and age, and study size. We also extracted information on cost of test, level of training and experience of technicians, and whether diagnosis was delivered at point of care.

We extracted TP, FP, TN and FN needed to populate the 2 x 2 tables. Authors of primary studies were contacted for unclear or insufficient data. Where possible, we obtained raw data from primary study authors to calculate values needed to populate the 2 x 2 contingency table. For studies that provided categorical data based on intensity of infection, we extracted numbers of index test positive and negative participants using the aforementioned thresholds. If two or more communities were involved in the study, data were extracted for each community, with a link to the parent study. Two authors extracted data using a pre-tested data extraction form and cross-checked for errors. Disagreements were resolved through discussion.

Data synthesis

Data were analysed and presented as sensitivity, specificity and false positive rate, with their 95 % confidence intervals (CI). The meta-analyses were performed using the bivariate model specified in Reitsma (2005)[28], using the Mada package in the R programming environment.[29] A continuity correction of 0.5 was added to all cell values. The function fits the bivariate model described by Reitsma[28] that Habord (2007)[30] showed to be equivalent to the Hierarchical Summary Receiver Operating Characteristics (HSROC) by Rutter (2001).[31] We specified the model as a linear mixed model with known variances of the random effects, similar to the computational approach by Reitsma (2005).[28] Variance components are estimated by restricted maximum likelihood (REML). In addition meta-regression is possible and the use of other transformations than the logit, using the approach of Doebler (2015).[29] The bivariate meta-regression was conducted using random effects approach incorporating the amount of correlation between sensitivity and specificity across studies. A p-value below 0.05 was used to test statistical significance. In order to remove the need to adjust for confounders, the analysis was restricted to studies that evaluated both index and reference standard tests in the same patients. Sub-group effects were investigated by stratifying the analyses by age (preschool children and infants, school- aged children and adults), sensitivity of reference standard and background endemicity measured by prevalence of the infection: low, moderate and high (for intestinal schistosomiasis) and low and high (for urinary schistosomiasis).

Assessment of heterogeneity and sub-group analysis

We assessed heterogeneity by inspecting the forest plots for overlapping CIs and outlying data; using the Chi-squared test with a p-value < 0.10 to indicate statistically significant heterogeneity based on commonly accepted DerSimonian & Laird test[32] that uses a more sensitive threshold of $p < 0.10$. The Cochrane collaboration recommends the use of p-value < 0.10 in statistical testing of heterogeneity in accuracy tests.[33] Therefore, we followed this convention, by defining heterogeneity as significant when $p < 0.10$ rather than the conventional level of p-value < 0.05. Where significant heterogeneity was detected, we carried out subgroup analyses based on clinical and methodological differences..

We applied an exploratory analysis[34] to investigate the performance of POC-CCA test with Kato-Katz as reference standard by means of a Latent Class Bivariate Model (LCBM). LCBM using Latent GOLD v 5.0[35] was fitted to capture the between-study variability in sensitivity and specificity by assuming that studies belong to one of several latent classes. Number of latent classes was selected using Akaike Information Criterion (AIC). This yielded both an interpretation and a description of the heterogeneity between studies.[34]

RESULTS

Of the 4,578 records retrieved by the search, twenty seven studies reported in 21 published papers met the inclusion criteria (Fig. 1 Flow diagram and Table 1 Summary of the characteristics of the included studies).

The studies were all conducted in Africa, 13 in East Africa[23,24, 36-46] six in West Africa[15-17,20,47-48] and one study in Southern Africa.[49] No study has been conducted in Central or North Africa and one study[22] was not assigned a specific country. Three of the studies were conducted in the 1990s and used the older version of CCA[15-17], the rest were conducted after the new millennium. None of the studies was a randomized control trial (RCT). Twenty-five studies assessed CCA for the diagnosis of *S. mansoni* and two for *S. haematobium*, and none for *S. japonicum*.

Two publications[20,48] that reported studies conducted in low, moderate and high endemicity settings were each managed as three separate studies. One study[39] that assessed adults and children and reported data separately was managed as two study-data points. One publication[22] was included because it reported primary data of a five-country study some of which were not available in the individual country studies. Some authors who were contacted provided additional data.[23, 24, 44]

POC-CCA VERSUS KATO-KATZ

a) *Single POC-CCA versus single Kato-Katz*

The accuracy of single POC-CCA test compared to single Kato-Katz reference standard (41.7 mg duplicate slides) for the detection of *S. mansoni* infection was investigated by seven studies[20,21,23,24,38,42,44,] from Kenya, Cameroon, Cote d'Ivoire, Uganda, Ethiopia, Kenya and Uganda, respectively. The meta-analysis showed sensitivity of POC-CCA test to be high [0.90, 95% CI 0.84-0.94, n=7] but low specificity [0.56, 95% CI 0.54-0.61, n=7] (Fig. 2). Analysing based on a summary of ROC showed diagnostic accuracy measured by area under curve (AUC) of 0.86 (Fig. 3). Clearly, there is wide variation in the false positive rate of POC-CCA for detecting *S. mansoni* infection as depicted by the individual eclipses under the ROC space.

b) *Single POC-CCA versus three KATO-KATZ*

Fourteen studies published in nine papers[20,21,24,32,38-41,47] compared single POC-CCA test with Kato-Katz test from three consecutive stools (41.7 mg duplicate) for the detection of *S. mansoni* infection and showed sensitivity of 0.85 [95% CI 0.80-0.88, n=14] and specificity 0.66 [95% CI 0.54-0.76, n=14]. The CIs of some of the studies were wide, suggesting small sample sizes. Whilst sensitiity estimates showed some consistency, there was huge variation in specificity in POC-CCA test.

For the rest of the analyses and results see Appendix.

DISCUSSION

This systematic review assessed accuracy of urine-based POC-CCA cassette test for the diagnosis of schistosome infections using stool-based Kato-Katz thick smear (for *S. mansoni* and *S. japonicum*,) or standard 10 mL urine filtration (for urinary schistosomiasis) as reference standard. The key findings show that single POC-CCA performs better than single Kato-Katz (duplicate 41.7 mg of stool).

Although most of the studies included in this review were conducted recently, after the new millennium, methodological quality did not reach expected standards. For example, none of the studies was RCT. Notwithstanding, given that the results have been consistent across studies and sensitivity analysis establishing that the results are robust to changes, as well as an independent study[50] showing no batch-to-batch variation with POC-CCA, negligible intra-reader variability (2%), and substantial agreement for inter-reader reliability of the test, it is unlikely that methodological quality will have caused substantial bias to affect the evidence presented.

All the studies were conducted in Africa, mostly from East Africa. Twenty five studies assessed POC-CCA for the diagnosis of *S. mansoni* infection and two for urogenital schistosomiasis with the majority involving children (preschool and school children). None of the studies assessed POC-CCA in the Americas (for the detection of *S. mansoni*) or Asia (for *S. japonicum* infection). Although this is not expected to affect generalizability of the review's conclusions, studies in other endemic settings or involving other schistosome species such as *S. mekongi* and *S. intercalatum* should be encouraged.[51]

The finding that CCA performs better in high compared to low endemicity settings has both practice and control implications as it suggests that CCA may not have an advantage over routinely used diagnostic tests which are being replaced. The lack of a true gold standard (i.e. a diagnostic test of 100 % specificity and 100 % sensitivity) a major problem for reliably assessing specificity of new tools is probably to be blamed for this observation. Therefore, to evaluate a new test, microscopy has to be performed on multiple samples in order to create a reliable 'parasitological gold standard'.[52] However, given the limitations of microscopy, combining the index test and the reference standard (considered to have higher sensitivity than the index test or the reference standard alone) with an individual considered to have the infection if positive for either Kato-Katz or CCA in the combined reference standard may be the best way of creating a 'true' gold standard.[52]

Although sensitivity and specificity of POC-CCA improve when assessed against an 'assumed gold standard' that combines the index test and reference standard,[52] comparing CCA versus combined CCA/Kato-Katz is far from ideal given that CCA test may add false positives (and negatives) and Kato-Katz will certainly add false negatives. Also, there is a possible interdependence or

measurement error effect and that the combination is not likely to present a real gold standard. An ideal situation would be to have different gold standards for sensitivity and specificity of CCA. For sensitivity, the gold standard would be several repeated Kato-Katz slides, ideally collected on different days. This is because the likelihood of a false positive result is limited with Kato-Katz given that eggs are not easily confused in faeces or urine. An alternative approach would be to use a 'predicted' gold standard at the population level (i.e. the pocket chart.[53]). For specificity of CCA, the best gold standard would be to use negative controls, i.e. persons from non-endemic areas. However, we did not retrieve any study that used negative controls.

There may be economies of scale in using combined gold standard tests, the cost of both tests may be less than the sum of the cost of either test in isolation. As this review attempted to explore all options regarding CCA test, we considered combined Kato-Katz/CCA as a distinct diagnostic test. Some primary studies presented the results for combined tests[49,54-56] implying that the authors of these studies considered the combined Kato-Katz/CCA option to be distinct. Although the combined Kato-Katz/CCA is not being employed in current control programmes, it is important to assess accuracy as this can become a diagnostic option in the future.

The absence of a clear reference standard creates an additional form of uncertainty in diagnostic test meta-analysis. Therefore, we investigated heterogeneity patterns through Latent Class Bivariate Analysis[34] that identified two latent classes using AIC and BIC criteria that demonstrated a substantial difference in diagnostic accuracy which could not be explained just by an implicit or explicit threshold effect. Subgroup analyses were needed and the results showed that number of urine samples for the test did not affect sensitivity and specificity in POC-CCA appreciably. Further exploratory analysis involving compilation of studies classified into latent classes was conducted to relate latent class to background factors. The results suggested that the number of urines, year the study was conducted and geographic location do not appear to affect accuracy. Age, endemicity and effect of treatment could not be thoroughly explored at this stage warranting further studies.

Predictive values are mathematically dependent on the pre-test prevalence of the infection.[33,34] Given that studies from different endemicity settings were combined in the meta-analysis, pooled sensitivity and specificty which are not usually affected by background prevalence were mostly used for presenting accuracy or test performance in this review. Nonetheless, sensitivity and specificity vary with threshold.

It is well known that after population-based treatment, most individuals not fully cured will have light infections, which can easily be missed by insensitive tests. The main purpose to evaluate POC-CCA after treatment would be to assess whether the test can pick up light infections. In our review we evaluated the effect of endemicity (i.e. light versus moderate/heavy infection) with the specific aim to gain knowledge about how the test would perform under real situations of low intensity of infection. Crudely speaking, moderate/heavy infections represent pre-control situations and light infections represent post-control. We believe that our approach for not including post-treatment data does not represent a serious limitation or a major drawback, but we appreciate the fact that important additional evidence would have come from real post treatment studies, if they were available, to compare post-treatment test performances with that of pre-control light infections. In fact, a bias could be introduced when doing test assessment after treatment, as the status of infection is already known. Notwithstanding, there may always be unknown confounding factors that we could not account for.

We have performed meta-analyses and subgroup analyses with few studies and are concerned about a risk of false reassurance. Given this problem, we caution the interpretation of the data due to incompleteness and false reassurance. Although there are limitations in the studies included in the review, the evidence presented appears to be strong and consistent. All the studies were based on fully paired (within-study) comparative accuracy studies and this review addressed a well-defined question in terms of participants, interventions, outcomes, and study design. The search included relevant electronic databases, and attempts were made to retrieve unpublished studies. Bias and errors were minimised during the review process with two reviewers independently selecting studies and extracting data, and presenting characteristics of the individual studies. Although formal assessment of quality of the included studies could not be done as part of this analysis, potential sources of heterogeneity were explored and reported. The review conclusions are consistent with the set objectives and evidence shown and are likely to be reliable.

Conclusions

POC-CCA test may represent an effective tool for mapping, monitoring and evaluation of *S. mansoni* control programmes given that it is more sensitive than the Kato-Katz test, commercially available and easy-to-use at low cost, but the evidence for *S. haematobium* may be inconclusive as it comes from only two studies. Whilst cost of test appears to be similar between POC-CCA and Kato-Katz (based on limited data), it takes relatively shorter time to prepare POC-CCA than Kato-Katz thick smear. Well design studies making head-to-head comparisons of cost of application of POC-CCA and evaluating effect of treatment are warranted to contribute additional evidence.

Conflict of interest

None declared by the authors.

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Authors Contribution

Drafted the manuscript (ADA, JM, PE, MR, SLDV), constructed the search strategy and searched for studies (ADA), selected studies (ADA, DB, JO, RHA and KMB), extracted data (ADA and DB), analysed data (JM and PE) and interpreted data (ADA, PE, JM, DB, SLDV). All authors helped review and accept content of the manuscript.

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Table 1 **Summary of characteristics of included studies in the systematic review and meta-analysis**

Sr. No	Study*	Country	Trial conducted	N**	Sample size	Characteristics of participants	Endemicity ***	Diagnostic criteria	Diagnosis at POC?	Trace as positive	Cost of test	Acceptability of test	Time for CCA preparation
1	Adriko 2014[24]	Uganda	Not reported	5	500	School children 7–13 yrs	8%, 23% & 36% for low, moderate and high endemicity settings, respectively	Index test: POC-CCA cassette (single urine) Alternative version CCA2 Reference standard: Kato-Katz (one, two, three stools, each 41.7 mg duplicate)	Yes	Both trace as +ve and trace as -ve	1.75 USD, cited from Colley 2013	Yes	Kato-Katz 60 min POC-CCA 5-20 min
2	Colley 2013[22]	Cameroon, Cote d'Ivoire, Ethiopia, Kenya, Uganda	2010	5	4305	School children, 9-12 yrs	15.1%, 25%, 38.4%, 43%, 47.9 for the different settings in the five countries	Index test: POC-CCA cassette (single urine) Reference standard: Kato-Katz (one stool, 41.7 mg duplicate)	No, laboratory	Yes	Not reported	Yes	Not reported
3	Coulibaly 2013[47]	Cote d'Ivoire	2011	2	242 (156 children dropout)	Preschool children <6 yrs	23.1%	Index test: POC-CCA cassette (two urines) Reference standard: Kato-Katz (two stools, 41.7 mg duplicate)	No, laboratory	Both trace a +ve and trac as -ve	Single POC-CCA (US$ 1.75) Single Kato-Katz (US$ 1.7)	Yes	POC-CCA 25 min Kato-Katz several hours
4	Dawson 2013[32]	Uganda	2011	Not reported	82	Preschool children < 6 yrs 46 children <3 yrs and 42 children 3-5 yrs	45%	Index test: POC-CCA cassette (one urine) Reference standard: Kato-Katz (two stools, 41.7 mg duplicate)	Yes	Yes	Not reported	Not reported	Kato-Katz 30 min
5	Erko 2013[38]	Ethiopia	2010/2011	2	620	School children: 8-12 yrs	34%	Index test: POC-CCA cassette (one, two, three urines) Reference standard: Kato-Katz (one, two, three stools, 41.7 mg duplicate) Gold standard: Combined POC-CCA cassette (three urines) and Kato-Katz (three stools, 41.7 mg duplicate)	No, laboratory	Yes	Not reported	Yes	Not reported
6	Koukounari 2013[39]	Uganda	2005	1	446	Children 7-16 yrs and adults 17-76 yrs	Not reported	Index test: POC-CCA cassette urine assays (25 mL of urine). Reference standard: Kato-Katz (three stools, duplicate)	No, laboratory	Yes	Not reported	Yes	Not reported
7	Sousa-Figueiredo 2013-study 1[23]	Uganda	2009	Not reported	333	Preschool children ≤6 yrs	7.2%	Index test: POC-CCA dipstick test (50 µl) Reference standard: Kato-Katz (one stool, 41.7 duplicate) Gold standard: SEA-ELISA (commercially available ELISA test), 75 ml of finger-prick blood	No, laboratory	Both trace as +ve and trace as –ve were reported	Not reported	Yes	Not reported

* Studies published in the same paper have been linked with the parent paper
**N= number of communities involved in the study
***Baseline prevalence of the infection according reference standard test.

Table 1 cont`d.

Sr. No	Study	Country	Trial conducted	N*	Sample size	Characteristics of participants	Endemicity **	Diagnostic criteria	Diagnosis at POC?	Trace as positive	Cost of test	Acceptability of test	Time for CCA preparation
8	Sousa-Figueiredo 2013-study 2[23]	Uganda	2009	Not reported	337	Preschool children ≤6 yrs	16.9%	Index test: POC-CCA dipstick test (50 µl) Reference standard: Kato-Katz (one stool, 41.7 duplicate) Gold standard: SEA-ELISA, 75 ml of finger-prick blood	No, laboratory	Both trace as +ve and trace as –ve were reported	Not reported	Yes	Not reported
9	Sousa-Figueiredo 2013-study 3[23]	Uganda	2009	Not reported	255	Preschool children ≤6 yrs	38.8%	Index test: CCA dipstick test (50 µl) Reference standard: Kato-Katz (one stool, 41.7 duplicate) Gold standard: SEA-ELISA (commercially available ELISA test), 75 ml of finger-prick blood	No, laboratory	Both trace as +ve and trace as –ve were reported	Not reported	Yes	Not reported
10	Tchuem Tchuente 2012-study 1[21]	Cameroon	2010/2011	1	765	School children 8–12 yrs	21%	Index test: POC-CCA cassette (one urine), CCA dipstick (designated CCA-L) Reference standard: Kato-Katz (three stools, 41.7 mg triplicate)	No, laboratory	Yes	Not reported	Yes	Not reported
11	Tchuem Tchuente 2012-study 2[21]	Cameroon	2010/2011	1	--	School children 8–12 yrs	41.8%	Index test: POC-CCA cassette (one urine), CCA dipstick (designated CCA-L) Reference standard: Kato-Katz (three stools, 41.7 mg triplicate)	No, laboratory	Yes	Not reported	Yes	Not reported
12	Tchuem Tchuente 2012-study 3[21]	Cameroon	2010/2011	1	--	School children 8–12 yrs	31.4%	Index test: POC-CCA cassette (one urine), CCA dipstick (designated CCA-L) Reference standard: Kato-Katz (three stools, 41.7 mg triplicate)	No, laboratory	Yes	Not reported	Yes	Not reported
13	Coulibaly 2011-study 1[20]	Cote d'Ivoire	2010	1	146	Children 8-12 yrs	32.91%,	Index test: POC-CCA cassette (one, two, three urines) Reference standard: Kato-Katz (one, two, three stools, 41.7 mg triplicate)	No, laboratory	Yes	Not reported	Yes	POC-CCA 20 min Kato-Katz 30 min
14	Coulibaly 2011-study 2[20]	Cote d'Ivoire	2010	1	130	Children 8-12 yrs	53.1%	Index test: POC-CCA cassette (one, two, three urines) Reference standard: Kato-Katz (one, two, three stools, 41.7 mg triplicate)	No, laboratory	Yes	Not reported	Yes	POC-CCA 20 min Kato-Katz 30 min
15	Coulibaly 2011-study 3[20]	Cote d'Ivoire	2010	1	170	Children 8-12 yrs	91.8%	Index test: POC-CCA cassette (one, two, three urines) Reference standard: Kato-Katz (one, two, three stools, 41.7 mg triplicate)	No, laboratory	Yes	Not reported	Yes	POC-CCA 20 min Kato-Katz 30 min
16	Shane 2011[42]	Kenya	2007	1	484	Children 1-15 yrs	38.8%	Index test: Cassette POC-CCA reagent strip (one urine), SWAP-specific IgG ELISA, Carbon CCA (25 mL of urine) Reference standard: Kato-Katz (three stool, duplicate)	No, laboratory		Not reported	Yes	CCA strips 40 min

Table 1 cont`d.

Sr. No	Study	Country	Trial conducted	N*	Sample size	Characteristics of participants	Endemicity **	Diagnostic criteria	Diagnosis at POC?	Trace as positive	Cost of test	Acceptability of test	Time for CCA preparation
17	Sousa-Figueiredo 2010[43]	Uganda	Survey in Lake Albert area 2007 and Lake Victoria 2009	Not reported	608 (245 mothers and 363 children)	Preschool children ≤6 yrs, mothers	In mothers (29.2% in Lake Victoria and 60% in Lake Albert) In children (16% in Lake Victoria and 43.3% in Lake Albert)	Index test: POC-CCA cassette (one urine) Single SEA-ELISA (fingerprick blood (~50 µl)), four slides of Kato-Katz Reference standard: Kato-Katz (two stools, duplicate) Gold standard: Combined CCA (one urine 50µl aliquot) and Kato–Katz (two stools, 41.7 mg duplicate).	No, laboratory	Yes	£1.60 for CCA	Yes	POC-CCA 20 min
18	Speich 2010[4]	Tanzania	2009	2	1,066	School children 6-20 yrs		Kato-Katz (one stool, 41.7 mg duplicate)	No, laboratory	N/A	Single Kato-Katz US$1.73 and duplicate US$2.06	Not reported	Kato-Katz 20-40 min
19	Standley 2010[44]	Kenya, Tanzania	2009	11	171	School children 6-17 yrs	68.6%?	Index test: POC-CCA urine-dipstick (reagent strips) Reference standard: Kato-Katz (one stool, 41.7 mg duplicate)	Yes	Yes	$ 2.3-2.8 USD per dipstick	Yes	Not reported
20	Midzi 2009[49]	Zimbabwe	2006	1	265	Pre- and school children 2-19 yrs	40.4%	Index test: Urine CCA reagent strips (25 mL of urine), Kato-Katz (one stool) and standard urine filtration (two consecutive days) Reference standard (gold standard): combined CCA and urine filtration	Yes, plus laboratory	CCA scored as weak +ve or strong +ve	Not reported	Yes	CCA strips 30 min
21	Stothard 2009[46]	Uganda	2009	1	242	Infants and preschool children ≤5 yrs	>50%	Index test: urine-based POC-CCA reagent strip; 75 µl for IEDM-ELISA (indirect egg detection method) Reference standard: Kato-Katz (two stools, 41.7 mg duplicate)	Yes	Not reported	Cost prediction	Yes	Not reported
22	Ayele 2008[36]	Ethiopia	Not reported	1	206	School children 4 – 21 yrs	47.6%	Index test: POC-CCA reagent strip Reference standard: Urine filtration technique (10 mL urine)	Yes	Not reported	CCA strip test, UD$4.95	Yes	CCA 25 min
23	Legesse 2008[41]	Ethiopia	2007	1	184	School children 5-22 yrs	36.4%	Index test: CCA reagent strip, Kato-Katz (one stool, duplicate slides) and Formol-ether concentration Reference standard: Kato-Katz (41.7 mg)	Yes	CCA scored as weak +ve or strong +ve	Not reported	Yes	Not reported

Table 1 cont`d.

Sr. No	Study	Country	Trial conducted	N*	Sample size	Characteristics of participants	Endemicity **	Diagnostic criteria	Diagnosis at POC?	Trace as positive	Cost of test	Acceptability of test	Time for CCA preparation
24	Legesse 2007[40]	Ethiopia	2007	1	251	Whole population (adults and children >5 yrs)	90% in school children	Index test: CCA urine assays (25 mL of urine), Kato-Katz (one stool, duplicate slides) and Formol-ether concentration Reference standard: Kato-Katz (one stool, duplicate slides)	No, laboratory	CCA scored as weak +ve or strong +ve	Not reported	Not reported	Not reported
25	De Clercq 1997a[57]	Mali	Not reported	2	Not stated (337 urine, 352 serum and 134 stool)	Whole population (adults and children) in irrigation area	99%	Index test: CAA- ELISA; CCA-ELISA (5 ml of blood); 2-fold dilution series of urine (1 ml) Reference standard: Kato-Katz (two stools, 41.6 mg duplicate)	No, laboratory	Not reported	Not reported	Yes	Not reported
26	De Clercq 1997b[58]	Mali	1993	4	Not stated (431 urine, 324 stool; 348 blood)	Whole population of adults and children	Not reported	Index test: CAA- ELISA (1 ml urine and 5 ml of blood); CCA-ELISA (1 ml urine and 5 ml of blood); urine filtration (10 ml); one Kato-Katz slide (41.6 mg) Reference standard: combined Kato-Katz (41.6 mg) and CAA-ELISA (1 ml urine and 5 ml of blood)	No, laboratory	Not reported	Not reported	Yes	Not reported
27	Kremsner 1994[17]	Cameroon	Not reported	1	148	School children 4–13 yrs	Not reported	Index test: CAA- EIA (urine and serum); CCA-EIA (urine and serum); thick blood smear (malarial parasites); combined reagent strip index (RSI) Reference standard: Kato-Katz, three (3) urine filtrations (10-50 ml)	No, laboratory	Not reported	Not reported	Yes	Not reported

Table 2a. **Tests classified as Latent Class 1**

Study ID	**Index Test**	**Reference Standard**
Coulibaly2011	POC-CCA cassette (one urine)	Kato-Katz (one stool)
Coulibaly2011-study1	POC-CCA cassette (one urine)	Kato-Katz (three stools)
Coulibaly2011-study1	POC-CCA cassette (three urines)	Kato-Katz (three stools)
Coulibaly2011-study2	POC-CCA cassette (one urine)	Kato-Katz (three stools)
Coulibaly2011-study2	POC-CCA cassette (three urines)	Kato-Katz (three stools)
Coulibaly2011-study3	POC-CCA cassette (one urine)	Kato-Katz (three stools)
Koukounari2013-study2	POC-CCA cassette (one urine)	Kato-Katz (three stools)

Table 2b. **Tests classified as Latent Class 2**

Study ID	Index Test	Reference Standard
Adriko2014	POC-CCA cassette (one urine)	Kato-Katz (one stool)
Adriko2014	POC-CCA cassette (one urine)	Kato-Katz (three stools)
Coulibaly2011-study3	POC-CCA cassette (three urines)	Kato-Katz (three stools)
Coulibaly2013	POC-CCA cassette (one urine)	Kato-Katz (three stools)
Coulibaly2013	POC-CCA cassette (two urines)	Kato-Katz (two stools)
Dawson2013	POC-CCA cassette (one urine)	Kato-Katz (two stools)
Erko2013	POC-CCA cassette (one urine)	Kato-Katz (one stool)
Erko2013	POC-CCA cassette (one urine)	Kato-Katz (three stools)
Erko2013	POC-CCA cassette (three urines)	Kato-Katz (three stools)
Koukounari2013-study1	POC-CCA cassette (one urine)	Kato-Katz (three stools)
Legesse2007	POC-CCA cassette (one urine)	Kato-Katz (one stool plus formol ether concentration)
Legesse2008	POC-CCA reagent (one urine)	Kato-Katz (one stool plus formol ether concentration)
Shane2011	POC-CCA cassette (one urine)	Kato-Katz (one stool)
Sousa-Figueiredo2013	POC-CCA cassette (one urine)	Kato-Katz (one stool)
Sousa-Figueiredo2013-study1	POC-CCA cassette (one urine)	Kato-Katz (one stool)
Sousa-Figueiredo2013-study2	POC-CCA cassette (one urine)	Kato-Katz (one stool)
Sousa-Figueiredo2013-study3	POC-CCA cassette (one urine)	Kato-Katz (one stool)
Standley2010	POC-CCA cassette (one urine)	Kato-Katz (one stool)
TchuemTchuente2012	POC-CCA cassette (one urine)	Kato-Katz (one stool)
TchuemTchuente2012-study1	POC-CCA cassette (one urine)	Kato-Katz (three stools)
TchuemTchuente2012-study1	POC-CCA cassette (three urines)	Kato-Katz (three stools)
TchuemTchuente2012-study2	POC-CCA cassette(one urine)	Kato-Katz (three stools)
TchuemTchuente2012-study2	POC-CCA cassette (three urines)	Kato-Katz (three stools)
TchuemTchuente2012-study3	POC-CCA cassette (one urine)	Kato-Katz (three stools)
TchuemTchuente2012-study3	POC-CCA cassette (three urines)	Kato-Katz (three stools)

Fig. 1**. Flow diagram of the study selection process**

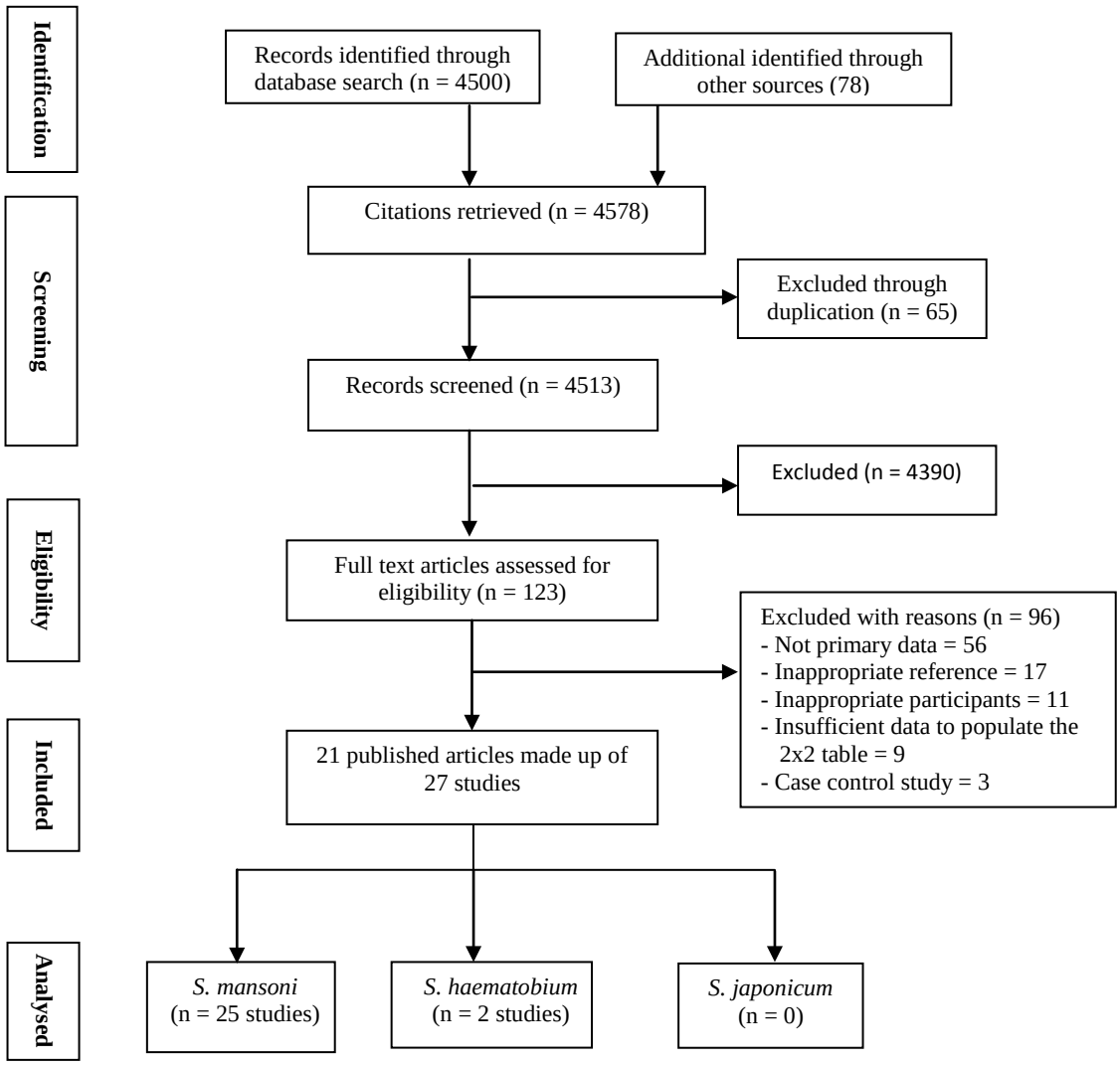
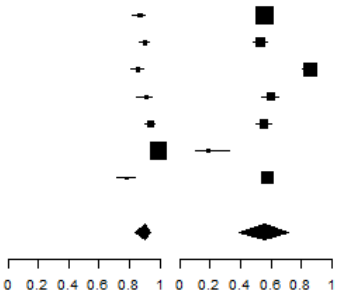


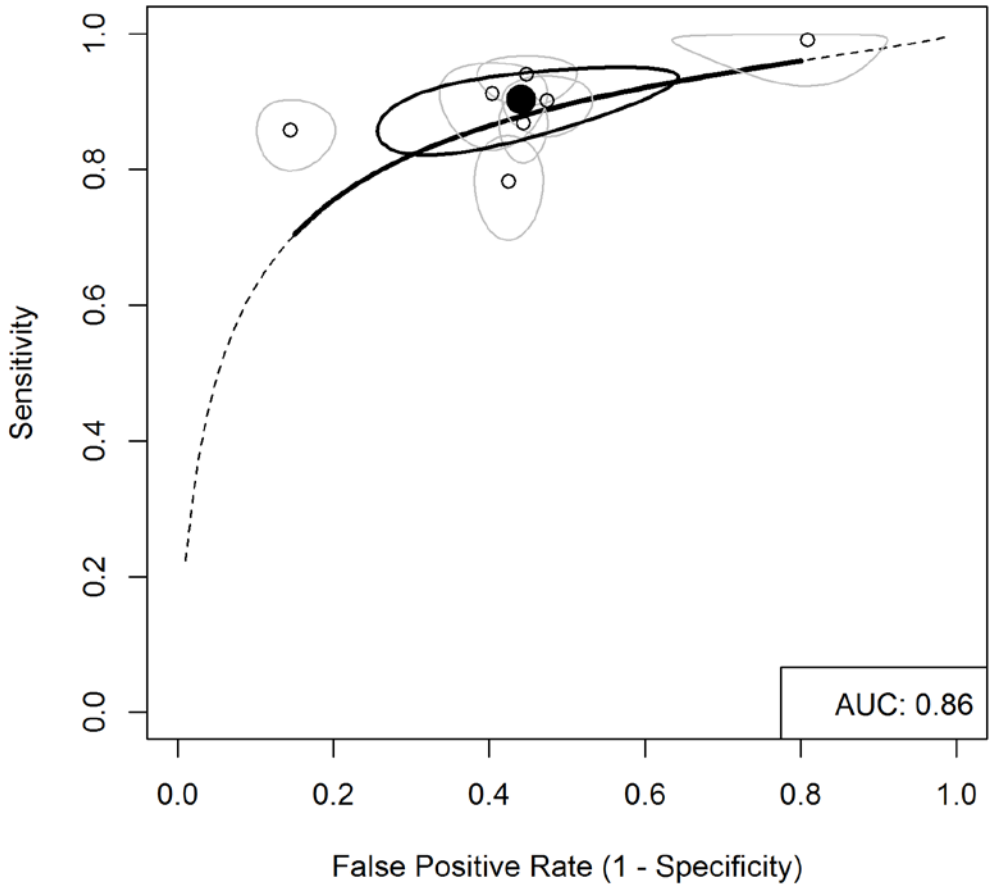
Fig. 2a. **Diagnostic accuracy of single POC-CCA versus single Kato-Katz as reference standard for the detection of *S. mansoni* infection**

Study	TP	FP	FN	TN	Sensitivity	Specificity
Shane 2011	231	664	35	833	0.87 [0.82, 0.90]	0.56 [0.53, 0.58]
Tchuem Tchuente 2012	247	208	27	231	0.90 [0.86, 0.93]	0.53 [0.48, 0.57]
Coulibaly 2011	230	42	38	249	0.86 [0.81, 0.89]	0.86 [0.81, 0.89]
Adriko 2014	114	119	11	176	0.91 [0.85, 0.95]	0.60 [0.54, 0.65]
Erko 2013	251	158	16	195	0.94 [0.90, 0.96]	0.55 [0.50, 0.60]
Standley 2010	105	38	1	9	0.99 [0.95, 1.00]	0.19 [0.10, 0.33]
Sousa-Figueiredo 2013	133	316	37	429	0.78 [0.71, 0.84]	0.58 [0.54, 0.61]
Pooled effect					**0.90 [0.84, 0.94]**	**0.56 [0.39, 0.71]**



For POC-CCA, trace was considered as positive.
Kato-Katz consisted of single stool of duplicate slides (41.7mg of stool sample each).
Data points for two studies[21,24] were extracted from another study[22] that reported primary data from a multi-country study in Africa.
Two of the studies[42,44] did not use POC-CCA cassettes but reagent strips that preceded the cassette formulation.

Fig. 2b. **Diagnostic accuracy of single POC-CCA versus single Kato-Katz reference standard for the detection of *S. mansoni* infection from SROC curve**



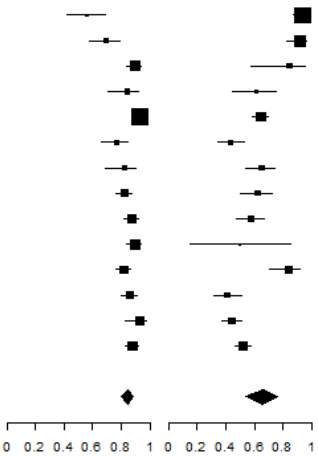
For POC-CCA, trace was considered as positive.
Kato-Katz consisted of single stool with duplicate slides (41.7mg of stool sample each).
Data points for two studies[21,24] were extracted from another study[22] that reported primary data from a multi-country study in Africa.
Two studies[42,44] did not use POC-CCA cassettes but reagent strips that preceded the cassette formulation.

Explaining the SROC curve

The SROC curves presented here are information rich, and contain a number of graphical features that each needs to be understood. The graph contains six separate types of information, represented by six separate types of graphical feature. Hollow circles represent the point estimates for the joint sensitivity and specificity of each individual study. Each of these hollow circles is surrounded by a light grey oval, which presents the 95% credible region associated with that particular study in ROC space. Similarly, the summary models, produced by pooling the estimates from each of the studies using a standard bivariate model, are presented both as a point estimate, represented by a solid black circle, and an associated 95% credible region, represented by the solid black line. In addition to this, the best estimate for how the sensitivity and specificity vary with the diagnostic threshold adopted is represented by a line which runs from the bottom left to the top right portion of the graph. The solid section of this line represents interpolated estimates, which 'fill in the gaps' between the studies available, whereas the dashed parts of this line are extrapolated from the data, and as such are more dependent on the modelling assumptions. Both the interpolated and the extrapolated parts of this line are needed in order to estimate the area under the curve (AUC), which is defined in the bottom right hand corner of the graph.

Fig. 2c. **Single POC-CCA test versus three Kato-Katz tests for the detection of *S. mansoni* infection**

Study	TP	FP	FN	TN	Sensitivity	Specificity
Coulibaly 2011-study 1	27	6	21	92	0.56 [0.42, 0.69]	0.94 [0.87, 0.97]
Coulibaly 2011-study 2	48	5	21	56	0.70 [0.58, 0.79]	0.92 [0.82, 0.96]
Coulibaly 2011-study 3	138	2	16	11	0.90 [0.84, 0.94]	0.85 [0.58, 0.96]
Dawson 2013	37	14	7	22	0.84 [0.71, 0.92]	0.61 [0.45, 0.75]
Erko 2013	306	103	23	188	0.93 [0.90, 0.95]	0.65 [0.59, 0.70]
Legesse 2008	60	60	18	46	0.77 [0.66, 0.85]	0.43 [0.34, 0.53]
Tchuem Tchuente 2012-study 1	41	31	9	57	0.82 [0.69, 0.90]	0.65 [0.54, 0.74]
Tchuem Tchuente 2012-study 2	145	26	31	43	0.82 [0.76, 0.87]	0.62 [0.51, 0.73]
Tchuem Tchuente 2012-study 3	136	37	19	50	0.88 [0.82, 0.92]	0.57 [0.47, 0.67]
Koukounari 2013-study 1	148	2	17	2	0.90 [0.84, 0.93]	0.50 [0.15, 0.85]
Koukounari 2013-study 2	189	7	41	37	0.82 [0.77, 0.87]	0.84 [0.71, 0.92]
Legesse 2007	130	59	21	41	0.86 [0.80, 0.91]	0.41 [0.32, 0.51]
Coulibaly 2013	52	104	4	82	0.93 [0.83, 0.97]	0.44 [0.37, 0.51]
Adriko 2014	155	140	21	153	0.88 [0.82, 0.92]	0.52 [0.47, 0.58]
Pooled effect					**0.85 [0.80, 0.88]**	**0.66 [0.54, 0.76]**



Kato-Katz consisted of three consecutive stools of duplicate slides each of 41.7 mg.

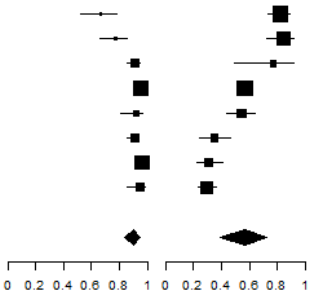
One of the studies[32] used Kato-Katz from two consecutive stools.

While other two of the studies[40,41] used an older version of POC-CCA reagent strips (manufactured by European Vertinary Laboratory, Woerden, Holland) and compared with combined Kato-Katz and Formal Ether concentration test as reference standard.

All other studies used POC-CCA cassette test (manufacturer: Rapid Medical Diagnostics, Pretoria, South Africa). Two studies published in one paper[39] involved separate data for children (7-16 years) and adults (≥ 17 years) so we reported them as independent studies in the analysis.

Fig. 2d. **Three POC-CCA tests versus Kato-Katz from three consecutive stools for the detection of *S. mansoni* infection**

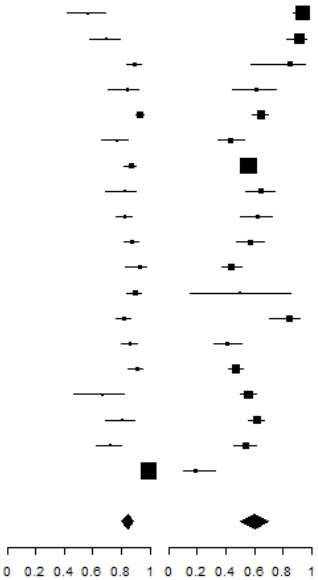
Study	TP	FP	FN	TN	Sensitivity	Specificity
Coulibaly 2011-study 1	32	17	16	80	0.67 [0.53, 0.78]	0.82 [0.74, 0.89]
Coulibaly 2011-study 2	51	9	15	48	0.77 [0.66, 0.86]	0.84 [0.73, 0.91]
Coulibaly 2011-study 3	138	3	13	10	0.91 [0.86, 0.95]	0.77 [0.50, 0.92]
Erko 2013	313	126	16	165	0.95 [0.92, 0.97]	0.57 [0.51, 0.62]
Tchuem Tchuente 2012-study 1	46	40	4	48	0.92 [0.81, 0.97]	0.55 [0.44, 0.65]
Tchuem Tchuente 2012-study 2	160	45	16	24	0.91 [0.86, 0.94]	0.35 [0.25, 0.47]
Tchuem Tchuente 2012-study 3	149	60	6	27	0.96 [0.92, 0.98]	0.31 [0.22, 0.41]
Coulibaly 2013	53	132	3	54	0.95 [0.85, 0.98]	0.29 [0.23, 0.36]
Pooled effect					**0.91 [0.84, 0.95]**	**0.56 [0.39, 0.72]**



One study[47] used duplicate instead of three POC-CCA cassette tests, the rest assessed three POC-CCA tests; the same study also used two consecutive stools for Kato-Katz tests, the rest of the studies used three consecutive stools.
For POC-CCA test, trace was considered as positive test.

Fig. 2e. **Assessment of diagnostic accuracy between single and multiple POC-CCA and single and multiple Kato-Katz tests for the diagnosis of *S. mansoni* infection**

Study	TP	FP	FN	TN	Sensitivity	Specificity
Coulibaly 2011-study 1	27	6	21	92	0.56 [0.42, 0.69]	0.94 [0.87, 0.97]
Coulibaly 2011-study 2	48	5	21	56	0.70 [0.58, 0.79]	0.92 [0.82, 0.96]
Coulibaly 2011-study 3	138	2	16	11	0.90 [0.84, 0.94]	0.85 [0.58, 0.96]
Dawson 2013	37	14	7	22	0.84 [0.71, 0.92]	0.61 [0.45, 0.75]
Erko 2013	306	103	23	188	0.93 [0.90, 0.95]	0.65 [0.59, 0.70]
Legesse 2008	60	60	18	46	0.77 [0.66, 0.85]	0.43 [0.34, 0.53]
Shane 2011	231	664	35	833	0.87 [0.82, 0.90]	0.56 [0.53, 0.58]
Tchuem Tchuente 2012-study 1	41	31	9	57	0.82 [0.69, 0.90]	0.65 [0.54, 0.74]
Tchuem Tchuente 2012-study 2	145	26	31	43	0.82 [0.76, 0.87]	0.62 [0.51, 0.73]
Tchuem Tchuente 2012-study 3	136	37	19	50	0.88 [0.82, 0.92]	0.57 [0.47, 0.67]
Coulibaly 2013	52	104	4	82	0.93 [0.83, 0.97]	0.44 [0.37, 0.51]
Koukounari 2013-study 1	148	2	17	2	0.90 [0.84, 0.93]	0.50 [0.15, 0.85]
Koukounari 2013-study 2	189	7	41	37	0.82 [0.77, 0.87]	0.84 [0.71, 0.92]
Legesse 2007	130	59	21	41	0.86 [0.80, 0.91]	0.41 [0.32, 0.51]
Adriko 2014	114	199	11	176	0.91 [0.85, 0.95]	0.47 [0.42, 0.52]
Sousa-Figueiredo 2013-study 1	16	137	8	172	0.67 [0.47, 0.82]	0.56 [0.50, 0.61]
Sousa-Figueiredo 2013-study 2	46	107	11	173	0.81 [0.69, 0.89]	0.62 [0.56, 0.67]
Sousa-Figueiredo 2013-study 3	71	72	28	84	0.72 [0.62, 0.80]	0.54 [0.46, 0.61]
Standley 2010	105	38	1	9	0.99 [0.95, 1.00]	0.19 [0.10, 0.33]
Pooled effect					**0.85 [0.80, 0.88]**	**0.60 [0.5, 0.69]**



Studies included in this analysis had both index and reference tests examined in the same participants at the same time.
Where a study assessed single, two, or three POC-CCA, the results of the single POC-CCA were selected for this analysis. Single POC-CCA test were chosen for the analysis from the three studies published in paper[21] and another study from Ethiopia.[38]
For POC-CCA test, trace was considered as positive.
Where a study assessed single, two or three Kato-Katz, single Kato-Katz (duplicate 41.7 mg) was chosen as reference standard in conformity with what WHO recommends within the MDA/PC Strategy. Single Kato-Katz was selected for the analysis from the study by Erko 2013.[38]
If different settings were involved in studies published in one article, the different settings were included as separate studies. Therefore, Coulibaly 2011[20] was classified as Coulibaly 2011 -study 1; Coulibaly 2011 -study 2; Coulibaly 2011 -study 3 and Tchuem Tchuente 2012[21] as Tchuem Tchuente 2012 -study 1; Tchuem Tchuente 2012 -study 2; Tchuem Tchuente 2012 -study 3).
Children and adults data reported separately were considered as separate datapoints in this analysis (Koukounari 2013[39]).

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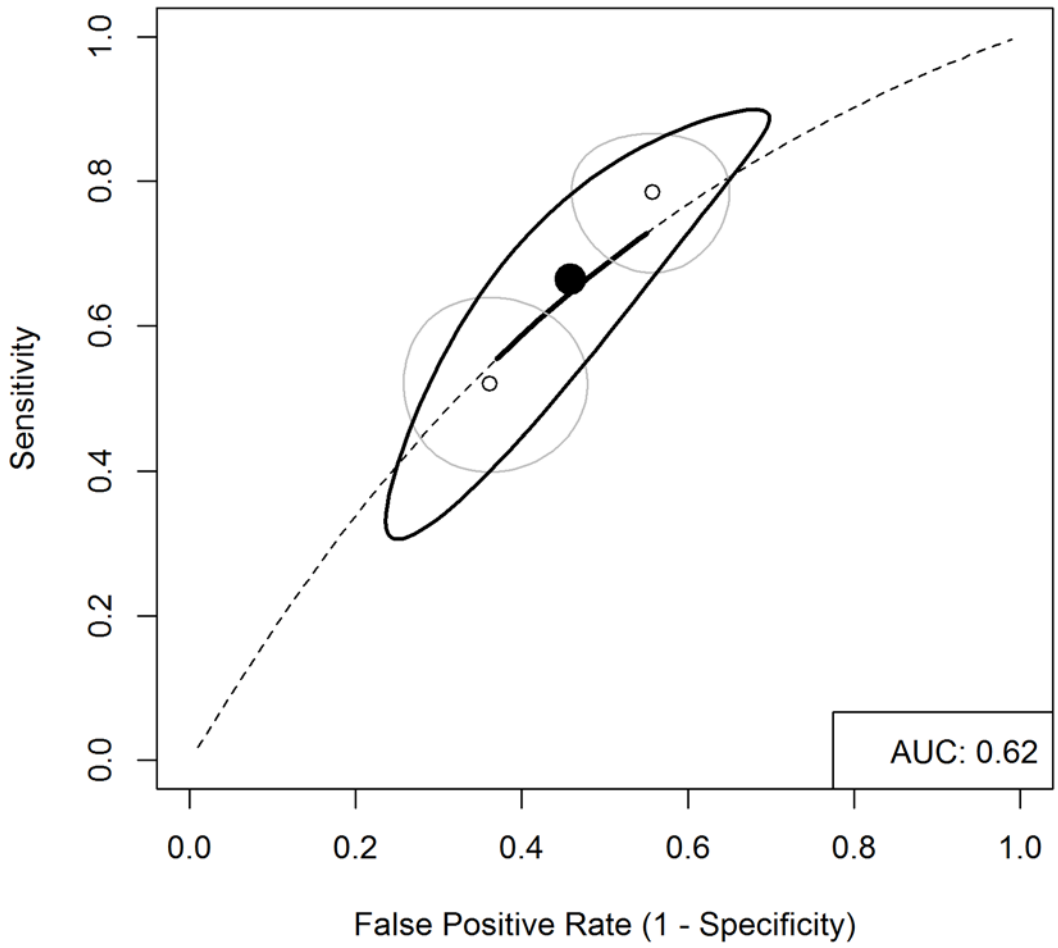
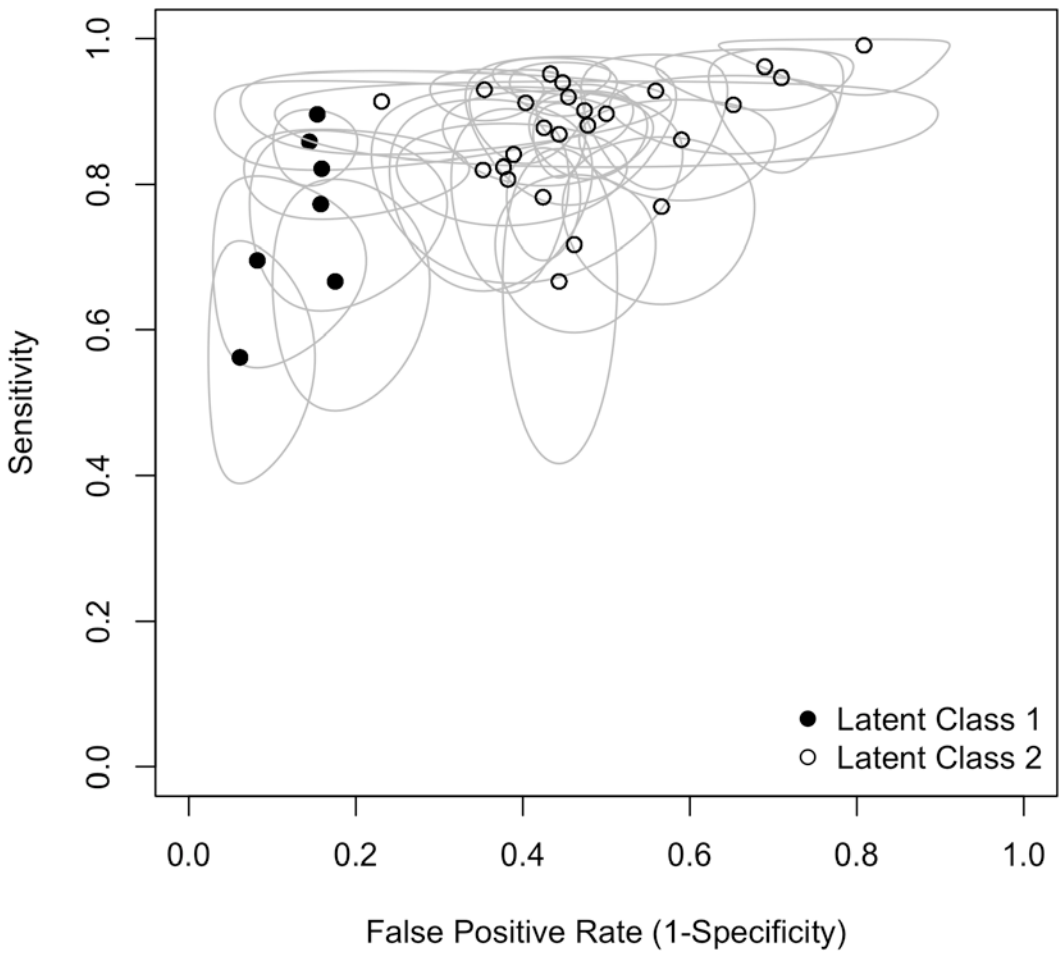
Fig. 3. **Performance of POC-CCA strips versus standard 10 mL urine filtration for the diagnosis of urogenital schistosomiasis**



The study[19] used reagent strips of POC-CCA with trace counted as positive test.

Fig. 4. **LCBM showing Latent Classes of POC-CCA test**



APPENDIX

POC-CCA VERSUS KATO-KATZ

c) *Three POC-CCA versus three Kato-Katz*

Eight studies, four from the same investigator from Cote d'Ivoire[20], three from the same author from Cameroon[21] and one from Ethiopia[24] assessed the performance of three POC-CCA tests versus Kato-Katz tests from three consecutive stools (duplicate 41.7 mg) for the detection of *S. mansoni* infection. The meta-analysis showed sensitivity of POC-CCA to be 0.91 [95% CI 0.84-0.95, n=8] and specificity 0.56 [95% CI 0.39-0.72, n=8] (Fig. 5). Sensitivities showed to be fairly consistent across studies but specificities showed wide CIs and variability across studies.

d) POC-CCA versus combined POC-CCA/Kato-Katz

Only one study[24] has investigated POC-CCA versus POC-CCA/Kato-Katz combined as reference standard for the diagnosis of *S. mansoni* infection and showed sensitivity of POC-CCA to be high (90%) with no false positives detected, giving a specificity of 100% (Table not shown). When the number of the index POC-CCA test was increased to three consecutive test, sensitivity increased to 96% (only marginally over single POC-CCA) and specificity remained unchanged (100%). The results should be treated with caution though as it came from only one study.

e) Global performance of POC-CCA versus Kato-Katz

Nineteen studies were combined in the meta-analysis for the assessment of single and multiple POC-CCA (up to three tests) versus single and multiple Kato-Katz (up to three tests) for the diagnosis of *S. mansoni* infection and the results showed pooled sensitivity and specificity of 0.85 [95% CI 0.80-0.88, n=9] and 0.60 [95% CI 0.50-0.69, n=9], respectively. CIs of most of the study estimates were wide reflecting possible small sample sizes. Sensitivities showed to be fairly consistent across studies, but specificities showed a considerable degree of variability across studies (Fig. 7).

POC-CCA REAGENT STRIP VERSUS 10 ML URINE FILTRATION TEST

The performance of POC-CCA was assessed for the detection of *S. haematobium* infection in two stuides in Ethiopia and Zimbabwe with mixed results: pooled sensitivity [0.66, 95% CI 0.37-0.87, n=2] and pooled specificity [0.54, 95% CI 0.34-0.73, n=2]. Given that only two studies were involved in the meta-analysis, the studies were conducted before 2007 and used relatively older version of POC-CCA reagent strips develped by the European Vertinary Laboratory, Woerden, Holland, the results should be treated with some caution. . In the study from Zimbabwe[49] when CCA was compared with combined CCA/urine filtration as reference standard, the results showed an improvement in sensitivity of CCA by about 10% from 79% to 88.2%. Similarly, accuracy of CCA test assessed from SROC curve showed low performanace from AUC curve (0.62, Fig. 3).

THE EFFECT OF ENDEMICITY, THRESHOLD AND AGE ON PERFORMANCE OF POC-CCA

a) *Background endemicity*

Four studies[20,21,23,24] assessed the effect of endemicity (low versus moderate-to-high) on diagnostic performance of POC-CCA in a meta-analysis and showed sensitivity for low endemicity was 0.69 [95% CI 0.56-0.79] and specificity 0.78 [95% CI 0.54-0.91], with somehow wide CIs , particularly

for specificity. Moderate to high endemicity showed relatively higher pooled sensitivity [0.81, 95% CI 0.76-0.85] and specificity [0.74, 95% CI 0.55-0.87], with sensitivities consistent across studies. Specificities showed somehow wide CIs around their effect estimates (Fig. not shown). The diagnostic accuracy as measured by AUC under the ROC space was 0.76 (Fig. not shown).

b) Threshold

The four studies conducted between 2009 and 2011, two from Uganda[23,24] one from a village along the Tanzanian-Kenyan border[44] and one study from Cote d'Ivoire[47] assessed the impact of POC-CCA test when trace was considered as positive for the diagnosis of *S. mansoni* infection. The studies showed an overall high sensitivity [0.93, 95% CI 0.74-0.99] but very low specificity [0.42, 95% CI 0.28-0.58]. Except the study by Sousa-Figueiredo 2013[23], sensitivities appeared to be consistent across studies. Although the pooled specificity was low, one study[44] reported unusually low specificity [0.19, 95% CI 0.10-0.33], but this is not expected to have affected the magnitude of the overall specificity as the weight contributed by the study was very small weight. Accuracy as measured by AUC under the ROC space was low 0.66 although the ROC curves and AUC estimates seem model dependent. Considering trace of POC-CCA test as negative decreased sensitivity by about 18% to 0.75 [95% CI 0.58-0.86, n=4] but improved specificity by about 37% to 0.79 [95% CI 0.73-0.85]. The study from the Kenya-Tanzania shoreline district of Lake Victoria[44] showed the biggest variation in both sensitivity and specificity.

c) Age

Only one study[39] involving children aged 7-16 years versus adults 17-76 years has assessed the impact of age on accuracy of POC-CCA using Kato-Katz test (two stools, 41.7 mg duplicate) as reference standard. The results showed that sensitivity (82%) and specificity (84%) were high for adults (Table not shown). When POC-CCA was assessed in children, sensitivity improved by about 8% to 90% but specificity decreased considerably to 50%. The results should be treated with caution though as it came from only one study with limited sample size.

SENSITIVITY ANALYSIS

We conducted sensitivity analyses to explore the effect of leaving a study from each of the analyses on the pooled AUCs which indicated that most analyses were not strongly influenced by any one particular study, with the exception of one study[20] in Analysis 1, whose exclusion reduced pooled AUC by -0.129 (around 15%); Tchuem Tchuente (2012)[21] in Analysis 6, whose exclusion reduced the pooled AUC by 0.091 (around 8%); and Sousa-Figueiredo (2013)[23] in Analysis 8, whose exclusion increased the pooled AUC by 0.069 (around 11%) (Figures not provided).

LATENT CLASS BIVARIATE ANALYSIS OF POC-CCA TEST

We applied an exploratory latent analysis[34] to investigate the performance of POC-CCA test with Kato-Katz as reference standard. Two latent classes have been identified using AIC with a substantial difference in specificity. The clustering of studies in two latent classes leads to conclude that the data showed substantial heterogeneity, suggesting that the observed variation of test outcomes cannot be explained by threshold effect alone. Latent Class 1 showed mean sensitivity of 76.4% [95% CI 72.3%-80.5%] and mean specificity of 84.2% [95% CI 79.9%-88.5%]. Latent Class 2 shows mean sensitivity of 89.6% [95% CI 88.0%-91.2%] and specificity of 47.1% [95% CI 43.2%-50.9%]. Hence, studies in the Latent Class 1 show a better performance (higher specificity at the price of small loss in sensitivity). Studies that used CCA versus combined CCA/KK tests were not inclued in the LCA.

From the output of the LCBM, urine samples do not appear to be related to the probability of a study being classified in a particular latent class thus increasing the number of urine samples do not result in a significant increase in test performance (Table 2a and Table 2b). The same holds for the number of stools in the Kato-Katz reference standard which was tested in the LCBM with the number of urine samples and stools as covariates, resulting in non-significant estimates. Sensitivities and specificities of studies classified in the two Latent Classes are plotted on the ROC space (Fig. 8).

ACCEPTABILITY OF POC-CCA TEST

Majority of participants in the studies that investigated acceptability stated that they considered the urine-based POC-CCA test as convenient and acceptable (21 out of 21 studies). The remaining six studies did not investigate this outcome (see Table 1). Still, there is paucity of comparative information on acceptability between POC-CCA and Kato-Katz tests.

COST OF TESTING

The study revealed paucity of information on cost of POC-CCA and Kato-Katz testing. Data from six studies showed that on average a single CCA will cost around US$ 1.70 for the diagnosis of schistosome infections, which is the same for a single Kato-Katz (US$1.70). The evidence presented should be treated with caution as the data appeared to have been quoted without formal cost analysis (Table 1). There are uncertainties about the prices of CCA but anecdotal data indicate that the price of CCA which is currently expensive and may not be met with national budget of countries in resource-limited settings, the price can be brought down to less than that of Kato-Katz depending on the quantity of kits purchased.

TIME FOR PREPARING TEST

Eleven studies reported time taken to prepare POC-CCA and Kato-Katz and showed that it took 5-25 minutes to prepare POC-CCA compared to 30-60 minutes for Kato-Katz test (Table 1). The older version of POC-CCA (CCA strips) took relatively longer time (40 minutes), but this is no longer in use.