Strengthening methods of diagnostic accuracy studies
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Circulating antigen tests and urine reagent strips for diagnosis of active schistosomiasis in endemic areas

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Abstract

Background: Point of care (POC) tests based on circulating antigen detection and urine reagent strips tests are being used as replacements of conventional microscopy in disease control programmes for schistosomiasis, as they are rapid, easier to use and interpret, and may have comparable, or higher, sensitivity to microscopy. As control programmes gain impetus and infection intensities decrease, higher sensitivities become a prerequisite for future diagnostics. This review focuses on infections by *Schistosoma mansoni* and *Schistosoma haematobium*, as these species account for the majority of Schistosoma infections and associated morbidity worldwide.

Objectives

To obtain summary estimates of the diagnostic accuracy of urine reagent strip tests for microhaematuria, proteinuria and leukocyturia in detecting active *S. haematobium* infection, with microscopy as the reference standard.

To obtain summary estimates of the diagnostic accuracy of circulating antigen tests: a urine POC Circulating Cathodic Antigen (CCA) test, a urine and serum CCA ELISA test and a urine and serum Circulating Anodic Antigen (CAA) test for the detection of active *Schistosoma* infection in geographical regions endemic for *S. mansoni* and/or *S. haematobium*, with microscopy as the reference standard.

To compare the accuracies of the above index tests

To investigate potential sources of heterogeneity on the diagnostic accuracy of the above tests

Methods: We searched the electronic databases: MEDLINE, EMBASE, BIOSIS, MEDION and Health Technology Assessment (HTA) without any language restriction; to 29th August 2013. In addition, references were tracked from all relevant papers from the initial database searches.
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**Selection criteria:** We included studies that used microscopy as the reference standard: for *S. haematobium*, microscopy of urine prepared by filtration, centrifugation or sedimentation methods; and for *S. mansoni*, microscopy of stool by Kato-Katz smear. We included cross-sectional studies, cohort studies and diagnostic case-control studies with cases and controls sampled from the same population, and only included studies carried out on participants residing in endemic areas.

**Data collection and analysis:** For each study, two review authors independently extracted data using a pretested form. The QUADAS-2 tool was used to assess the methodological quality of included studies. We performed a meta-analysis for test types if we had results from four different studies or more and there was no substantial heterogeneity as demonstrated in the receiver operating characteristic (ROC) plots. By considering the variability of test thresholds we used the hierarchical summary receiver operating characteristic (HSROC) model for all eligible tests except the CCA POC for *S. mansoni* where we used the bivariate random effects model to perform the meta-analysis. Where sufficient data were available, we investigated the sources of heterogeneity. We also performed indirect test comparisons (all studies) and direct test comparisons (paired studies, in the same individuals).

**Results:** We included 86 studies. All but one study were carried out in Africa and all but one in field settings. The median prevalence for *S. haematobium* infection was 42% (range 21% to 57%) and that of *S. mansoni* infection, 44% (range 27% to 57%). About 82% (n=70/86) of the studies did not state the treatment status of participants with praziquantel prior to the baseline study. We performed overall meta-analyses for 5 test types: microhaematuria, proteinuria, leukocyturia, CCA POC test for *S. haematobium* and CCA POC test for *S. mansoni*.

Among the tests to detect *S. haematobium* infection, microhaematuria had the highest sensitivity (76% (72 to 80%)) and specificity (86% (83 to 89%)). The average sensitivity and specificity for the other tests (in decreasing order of sensitivity) were: 61% (53% to 69%) and 83 % (77% to 88%) for proteinuria, 58% (44% to 71%) and 61 % (34% to 88%) for leukocyturia and 39% (6% to...
73%) and 78% (55% to 100%) for the CCA POC test for *S. haematobium*. The difference in overall test performance (accuracy) between the urine reagent strip for microhaematuria and proteinuria was not statistically significant when the comparisons were between separate populations (p=0.21) and when directly compared in the same individuals (paired studies (p=0.17).

To detect *S. mansoni* the average sensitivity and specificity for the CCA POC test were 87% (85% to 90%) and 61% (51% to 70%) respectively.

When the tests were evaluated against the higher quality reference standard (i.e. when multiple samples were analysed), the sensitivity was lower for microhaematuria (71% vs. 76%) and proteinuria (49% vs. 61%) in comparison to a poor quality reference standard. The specificity of these tests was comparable. In contrast, the sensitivity and specificity of CCA POC for *S. mansoni* were both higher (88% vs. 86% and 69% vs. 62% respectively) when measured against a higher quality reference standard.

In the light intensity subgroup the sensitivity was slightly lower for microhaematuria (73% vs. 76%) but similar for proteinuria compared to results of the overall analysis. There was insufficient data to estimate the sensitivity of CCA POC for *S. mansoni* in light intensity settings. Limited data restricted our evaluation of the circulating antigen ELISA tests. The risk of bias assessment was largely unclear due to poor reporting of items in the included studies.

**Authors’ conclusions:** Among the evaluated tests for *S. haematobium* infection, microhaematuria detected the largest proportion of infections and non-infections identified by microscopy. This test could continue to serve as a replacement test for microscopy for initial mapping or estimation of *S. haematobium* infection, particularly in endemic areas with a moderate to high prevalence of infection. The CCA POC test for *S. mansoni* detects a very large proportion of infections identified by microscopy but misclassifies a large proportion of microscopy negatives as positives in endemic areas with a moderate to high prevalence of infection. This may be because the test is
potentially more sensitive than microscopy. This test could be used for initial mapping or estimation of *S. mansoni* infection, but its positive results should be interpreted with care as they may be false positives.

In the absence of a suitable reference standard for schistosomiasis, more studies comparing the accuracy of microscopy, circulating antigen tests and urine reagent strips to other proposed reference standards are needed to reliably recommend a suitable replacement for microscopy in practice.
8.1 Background

Schistosomiasis, also known as bilharzia, is the second major parasitic disease affecting tropical and subtropical regions after malaria. It is caused by trematode worms of the genus *Schistosoma*(1). The latest estimates show that schistosomiasis is endemic in 76 countries, with 779 million people at risk of infection with approximately 207 million people currently infected. Sub-Saharan Africa (SSA) accounts for more than 90% of current cases of schistosomiasis (1)(2)(3). The global burden of disease was estimated at 13 to 15 million disability adjusted life years (DALYs) lost due to schistosomiasis globally in 2004 (4).

Five main schistosome species are known to infect man, of which *Schistosoma mansoni*, *Schistosoma haematobium* and *Schistosoma japonicum* have the greatest impact on morbidity (5). The focus of this review will be on diagnosing infection due to *S. mansoni* and *S. haematobium*, as they are more widespread globally and account for the majority of infections and associated morbidity worldwide. These species cause intestinal schistosomiasis and urinary schistosomiasis respectively.

Currently, there is no vaccine to protect against schistosomal infection (6,7). If left untreated, schistosomal infections may result in chronic disease. The current drug of choice is praziquantel, which is cheap, safe and with few side effects, costing less than USD 0.15 per treatment (1,8). Mass praziquantel treatment of populations at risk of infection is now routine in many endemic areas (3,8). Re-infections rapidly occur due to recurrent direct contact with water bodies infected with schistosomal parasites(7–9). There is still no strong evidence of clinically relevant drug resistance (10–14). There are however reports of heterogeneities in egg reduction rates and systematic non clearers of infection after treatment with praziquantel (15–17). In the long run, mass treatment has limitations related to cost effectiveness (18), poor sustainability (19), poor drug compliance by individuals (20,21) and increased drug selection pressure (14).
Accurate and affordable diagnostic tools are essential for targeted treatment and to maximize the success of control of schistosomiasis in endemic areas, as well as a prerequisite for monitoring drug efficacy. Diagnosis of schistosomiasis can be performed directly or indirectly. Direct methods include detection of schistosome eggs in urine or stool by microscopy, detection of schistosome antigens in serum or urine samples, or detection of *Schistosoma*-specific DNA in urine, stool or blood. Indirect methods include use of questionnaires, biochemical tests (urine reagent strips for microhaematuria/proteinuria/leukocyturia), antibody tests, ultrasonography, computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, endoscopy and cystoscopy (1,22–26).

There is currently no recommended gold standard for the detection of schistosomiasis. Microscopy is the most widely used test for diagnosing schistosomiasis and though imperfect is commonly used as the reference standard in practice. Its sensitivity has been shown to vary with the intensity of infection, prevalence of infection, sample preparation techniques, stool consistency, and circadian and day-to-day variation of egg counts in stool and/or urine (22,23,27–31). This becomes particularly pertinent as control programmes progress and sensitivity of microscopy decreases due to reductions in infection intensities. Repeated measurements over multiple days from multiple samples and/or taking multiple smears/ slides from each sample has been shown to increase sensitivity (31–34), however this increases the time taken to perform the survey and therefore becomes logistically expensive (30,35).

### 8.1.2 Index test(s)

Urine reagent strips and circulating antigen tests are being used as alternatives to microscopy for diagnosis of schistosomiasis. Compared to microscopy, urine reagent strips used to detect micro-haematuria or proteinuria as a proxy for *S. haematobium* infection are cheap, quick, easy to use (36,37), have no technical requirements and are less influenced by the circadian production of schistosome
eggs (38). Furthermore, some studies have shown that the sensitivity of these strips is higher than urine filtration (39,40) and that a single test with haematuria strips is more sensitive than a single test with urine filtration (41). These features make these strips suitable for screening of urogenital schistosomiasis in the field.

Circulating antigen tests (circulating anodic antigen (CAA) and circulating cathodic antigen (CCA)) have also been evaluated as replacements of microscopy for the diagnosis of infections due to *S. haematobium* and *S. mansoni*. These tests can differentiate between active and past infections as the circulating antigens are probably only present when there is active infection (24). Since circulating antigens are released from living worms, antigen levels may correlate directly with parasite load, whilst microscopy does not. This may make the CCA POC test useful in monitoring the dynamics of worm burdens and clearance of the worms after treatment (8,26). However, their sensitivity has been shown to vary with disease prevalence and intensity of infection (42–49).

This review evaluates urine CCA POC test, urine CCA and CAA enzyme-linked immunosorbent assay (ELISA) and serum CCA and CAA ELISA. To note, the urine CCA dipstick was developed based on the performance of the ELISA format (37). The urine CCA ELISA was found to have the best diagnostic performance, followed by the serum CAA assay for *S. mansoni* (30,50,51). Therefore, although not rapid tests, the accuracy measures of the ELISA tests will be systematically assessed as the summary measures obtained may guide the ongoing development of improved POC tests.

So far, a range of accuracy measures have been reported for urine reagent tests and for circulating antigen tests. The diagnostic and treatment strategies in endemic areas with these tests vary and depend on financial and human resource capacity.

**8.1.3 Clinical pathway**

Patients suspected of having active *S. haematobium* or *S. mansoni* infections in endemic settings.
8.1.4 Prior test(s)

The current practice in endemic settings is using urine reagent strips as a replacement to microscopy or as a triage test (before microscopy) or using circulating antigen tests as a replacement to microscopy. In line with the practice in disease control programs we focus on the role of these tests as alternatives to microscopy. We will not consider prior testing with other tests as this is rarely done in public health programs.

8.1.5 Role of index test(s)

We are interested in the following purposes for testing:

a) The reagent strips to detect microhaematuria, proteinuria or leukocyturia as a replacement test for microscopy for S. haematobium infection.

b) The CCA-point of care test as a replacement test for microscopy for S. haematobium or S. mansoni infection.

8.1.6 Alternative test(s)

Apart from the two test types mentioned above, there is a range of other tests that can be used to screen for schistosomiasis. However, these are all used in different situations and different circumstances than the above mentioned tests.

Questionnaires have been used for the initial rapid screening of urinary schistosomiasis in high risk communities in endemic areas(22,52,53) . These questionnaires rely on self-reporting of blood in urine. Studies have shown that the use of questionnaires demonstrate moderate-to-high sensitivities and specificities when screening individuals for urogenital schistosomiasis in high prevalence areas but low sensitivity and specificity in low prevalence areas. (37,52). Questionnaires for intestinal schistosomiasis have been shown to be less sensitive and specific than those for urogenital schistosomiasis (9,37). The symptoms of intestinal schistosomiasis are associated with many other diseases, which often overlap in ranges. With coinfection the norm rather than a rare occurrence, the questionnaires are hence less specific. The accuracy of
questionnaires has also been shown to be influenced by age and gender. If used repeatedly in the same area, respondents are prone to give biased answers as they know the consequence of the answers they give. Thus, recall bias may interfere with the accuracy of the test. Consequently, relying on questionnaires may become ineffective and makes this screening method unsuitable even for follow-up of patients after treatment (54–56). As questionnaires are mainly recommended for initial rapid screening and not routine screening of schistosomiasis, they will not be evaluated in this review.

Serology tests are alternative tests in the diagnosis of schistosomiasis. These tests detect antibodies against worm antigens, egg antigens (soluble egg antigens (SEA)) or eosinophil cationic proteins (ECP) (22,57,58). Available methods include ELISA, indirect immunofluorescence assays (IFA) and indirect haemagglutination assays (IHA). Antibody tests demonstrate high sensitivity even in areas with light infections and therefore can be used in areas with low endemicity. However these tests fall short in distinguishing current active infections from past infections, have low specificity in endemic areas due to cross reactivity with antigens of other helminths and often antibody levels remain elevated after treatment, therefore these tests lead to many false positive results (24,26). Antibody tests may have a role in checking if there is any maintained exposure to schistosomiasis in areas where they are moving towards elimination (8).

The ECP test is an indirect marker of *S. haematobium* infection and related morbidity (59,60). Other test examples include rectal biopsy (58), cystoscopy and endoscopy, radiological methods (25), FLOTAC; a novel faecal egg count technique (61,62), and molecular tests using polymerase chain reaction (PCR)(63–65). However these tests may be expensive or require trained laboratory personnel and elaborate laboratory infrastructure.

**8.2 Rationale**

For improved mapping, to ensure effective selective (or targeted) treatment and for accurate data on treatment success with praziquantel, appropriate diagnostic
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tests are urgently required. When considering a test for diagnosing schistosomiasis, a test with a high sensitivity is paramount especially when monitoring infection within a disease control programme. False negative results lead to missed treatment and subsequently more advanced disease, or if occurring after praziquantel treatment, may lead to overestimated cure rates and potentially undetected cases of praziquantel resistance and its spread. High specificity is also required as unnecessary treatment due to false positive results could reduce cost effectiveness in current control programme strategies through potential inaccurate classification of prevalence levels, or in the future in targeted treatment control programmes (9). On the other hand, a test for mapping of disease (to get an estimation of disease prevalence in an endemic area) may not need as high a sensitivity and specificity as that required for monitoring of disease.

There is currently no recommended gold standard for the detection of active schistosomiasis. However, because in practice, microscopy is the most commonly used test and often used as the reference test in studies, we selected it for use as the reference standard to detect *S. haematobium* and *S. mansoni* within this review. The primary concern with microscopy is about missing infected cases (due to its low and varied sensitivity) especially in areas with a low intensity of infection. This means that truly infected cases may be missed and misclassified as non-infected by microscopy. Therefore when comparing an index test against microscopy, the number of false positives (potentially true cases classified as positive by the index test and classified as negative by the reference test) may be high and the index test may present with a low specificity. Increasing the sensitivity of microscopy by having multiple measurements may reduce the number of true cases wrongly classified as non-infected by microscopy. An index test compared against a more sensitive reference test (microscopy with multiple measurements) may have a higher specificity because the number of false positives will be low. Our review will therefore also investigate the effect of the quality of the reference standard on the sensitivity and specificity of the index tests being evaluated.
In this case, a test being considered as a replacement for microscopy should have a comparable sensitivity and/or be less costly, portable, faster and easier to use and/or interpret, and/or be less demanding logistically. POCs based on circulating antigen detection and biochemical urine reagent strips in particular are being used (or developed) in disease control strategies as they are easy to use and interpret, require minimal laboratory infrastructure, are cost-effective, reduce patient waiting time and potentially therefore reduce loss to follow up cases and may have comparable or higher sensitivity to microscopy (66). The results of this review may guide policy makers on the appropriate diagnostic tests to use and help identify research gaps in diagnostic tests for schistosomiasis in endemic areas.

8.3 Objectives

In order to make recommendations and inform policy makers on which tests to use and to identify research gaps, our primary objectives were:

To obtain summary estimates of the diagnostic accuracy of urine reagent strip tests for microhaematuria/ proteinuria/ leukocyturia in detecting active *S. haematobium* infection, with microscopy of urine as the reference standard.

To obtain summary estimates of the diagnostic accuracy of CCA POC test and ELISA for CCA or CAA in serum or urine, for the detection of active *Schistosoma* infection in geographical regions endemic for *S. mansoni* and/or *S. haematobium* with microscopy of stool or urine or both, as the reference standard.

To compare the accuracies of the above index tests

8.3.1 Secondary objectives

To investigate whether age and gender of participants, positivity thresholds, prevalence of infection, intensity of infection, quality of the reference standard, effect of praziquantel treatment, infection stage, mixed infections and whether the methodological quality of the included studies can explain the observed heterogeneity in test accuracy estimates.
8.4 Methods

8.4.1 Criteria for considering studies for this review

Types of studies

We included primary observational studies that compared the results of one or more of the index tests with the reference standard. These studies could be cross-sectional in design, cohort studies or diagnostic case-control studies with cases and controls sampled from the same patient population.

We included studies that provide data for patients. Only studies in which true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN) were reported or could be extracted from were included.

We excluded case-control studies with healthy controls, controls with alternative diagnoses (patients with diseases with similar signs and symptoms of schistosomiasis) or controls from non-endemic areas as specificity may be overestimated. We also excluded studies, which only enrolled proven cases of schistosomiasis as sensitivity may be overestimated.

Participants

Participants had to be individuals residing in regions where *S. haematobium* and *S. mansoni* infections were endemic. We excluded articles that studied travelers originating from non-endemic countries as they were typically screened with other tests such as antibody tests.

Index tests

We included studies that evaluated the following tests:
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*Urine reagent strip tests*

A urine reagent strip test is a biochemical semiquantitative test. It is regarded as an indirect indicator of *S. haematobium* infection or morbidity as it detects microhaematuria, proteinuria or leukocyturia (white blood cells in urine) that can develop as a consequence of schistosomal infection (67). They are cheap and easy to use for rapid screening of urinary schistosomiasis (1,5,22).

The results for urine reagent tests measuring haematuria are scored as 0 (negative), trace positive (tr), + (5 to 10 erythrocytes/μl), 2++ (10 to 50 erythrocytes/μl) or 3+++ (50 to 250 erythrocytes/μl). For proteinuria results are scored as 0 (negative), trace positive (tr), + (30 mg protein/dL), 2++ (100 mg protein/dL) or 3+++ (500 mg protein/dL) (38).

*Antigen tests*

These tests are based on the detection of schistosome antigens in serum and urine of individuals (1,5,9). The main circulating antigens are adult worm gut-associated circulating antigens with CAA and CCA being the main focus of research.

The CCA dipstick is scored according to the test band reaction intensity as negative (-), trace positive (tr), single positive (+), double positive (++) and triple positive (+++) (46). ELISA results are continuous and positivity thresholds may vary. To estimate the accuracy of ELISA tests, ELISA will have to have been evaluated against the reference standard only.

**Target conditions**

*Active infection with S. haematobium*

*Active infection with S. mansoni*
Reference standards

*S. haematobium*

For diagnosis of *S. haematobium* infection, the reference standard is microscopy of urine for the examination of schistosome eggs. To increase sensitivity, urine samples can be concentrated by sedimentation, filtration or centrifugation techniques (5) or more samples can be examined (22). We therefore included studies that use all these concentration techniques and in order to estimate the effect of the quality of the reference standard, we accepted studies using microscopy on a single urine sample (poor quality reference standard) and studies performing microscopy on multiple urine samples (higher quality reference standard).

*S. mansoni*

For diagnosis of *S. mansoni* infection, microscopic examination of schistosome eggs in stool is the reference standard. Sensitivity is increased by preparing a faecal thick smear using the Kato-Katz (KK) method (5) or by examining multiple stool samples (22). In order to estimate the effect of the quality of the reference standard, we accepted studies using microscopy on a single stool sample (poor quality reference standard) and studies performing microscopy on multiple stool samples (higher quality reference standard).

Importantly, some regions experience mixed infections of *S. haematobium* and *S. mansoni*. In such situations, both microscopy of stool and urine samples need to be carried out to confirm infections.

8.4.2 Search methods for identification of studies

8.4.2.1 Electronic searches

We searched the electronic databases, MEDLINE, EMBASE, BIOSIS, MEDION and HTA (Health Technology Assessment). The MEDLINE search strategy is outlined in Appendix 1. We further translated the MEDLINE search to EMBASE and BIOSIS
databases to identify additional records. To avoid missing studies, we did not use a diagnostic search filter. We performed the searches on 12th January 2012 and repeated them on 16th November 2012 and 29th August 2013.

8.4.2.2 Searching other resources

We looked through reference lists of relevant reviews and studies, websites of the World Health Organisation (WHO), Schistosomiasis Control Initiative (SCI) and Schistosomiasis Consortium for Operational Research and Evaluation (SCORE). Where possible, we contacted authors for extra information.

8.4.3 Data collection and analysis

8.4.3.1 Selection of studies

Two independent reviewers first looked though titles and abstracts to identify potentially eligible studies. Full text articles of these studies were obtained and assessed for study eligibility using the predefined inclusion and exclusion criteria by two independent reviewers. Disagreements were resolved through discussion and by a third reviewer when necessary.

8.4.3.2 Data extraction and management

Two independent authors extracted data onto a data extraction form.

The following data was extracted:

- authors, publication year, journal;
- study design;
- study participants - age, sex;
- prevalence of schistosomiasis;
- treatment status of participants with praziquantel - pre-treatment or post treatment;
- reference standard (microscopy), including number of samples per individual, and exact volume of stool/urine examined;
• index tests - urine and serum circulating antigen tests (CCA and CCA), urine reagent strips;
• urine reagent strips - signs measured (microhaematuria, proteinuria, leukocyturia);
• sample preparation techniques - time of day urine/stool sample was taken, intensity of infection - egg counts in urine and stool by microscopy;
• presence of missing or unavailable test results;
• number of TP, FN, FP and FN.

8.4.4 Assessment of methodological quality

We used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool to assess the risk of bias and concerns for applicability of the included studies (68). Disagreements were resolved through consensus or by a third reviewer. We extracted data using signaling questions and also scored for risk of bias and concerns for applicability under the four main domains: Patient selection, index test, reference standard and patient flow.

8.4.5 Statistical analysis and data synthesis

8.4.5.1 Comparisons of index test with the reference standard

We analysed data for the two target conditions (S. haematobium and S. mansoni) separately. Only one included study (69) evaluated the ability of a test to detect either S. haematobium and/or S. mansoni in an area of mixed infection.

Of those studies reporting sufficient data for calculating sensitivity and specificity, we plotted their sensitivity and specificity (and their 95% confidence intervals (CI)) in both forest plots and receiver operating characteristic (ROC) space using the statistical software Review Manager 5.2. We performed a meta-analysis using the statistical software SAS version 9.2 for test types that had sufficient data points (4 or more data points) to be pooled by the statistical models and those that did not demonstrate substantial heterogeneity in ROC space (70). These tests were the reagent strip for microhaematuria, reagent
strip for proteinuria, reagent strip for leukocyturia, the CCA POC test for *S. haematobium* and CCA POC test for *S. mansoni*.

The choice of the statistical model to perform the overall meta-analysis depended on the variability of the positivity thresholds as discussed below. The data for urine reagent strips and urine CCA POC tests were ordinal. These tests are typically scored as 0, trace, 1+, 2+ and 3+ or as 0, 1+, 2+ and 3+.

When the data of a test had multiple thresholds we used the Hierarchical Summary Receiver Operating Characteristic model (HSROC) to perform the overall meta-analysis. This model estimates the underlying ROC curve which describes how sensitivity and specificity of the included studies trade-off with each other as thresholds vary. It allows for variation in the parameters; accuracy, thresholds between studies and the shape of the underlying ROC curve (70,71). Because this method models sensitivity and specificity indirectly, we calculated the average sensitivities and average specificities from the output of the model.

When the data of a test had one or a common threshold, we used the bivariate random effects model to perform the overall meta-analysis. This method models sensitivity and specificity directly at a common threshold (70,72).

We included all studies, whether a positivity threshold was included or not, in the overall meta-analysis. We assumed that different thresholds were used for the studies that did not report their thresholds and used the HSROC model to perform the overall meta-analysis. For the urine reagent strips for microhaematuria and proteinuria, many studies did not report a positivity threshold (n=41 for microhaematuria and n=25 for proteinuria). Some studies (n=2) provided datapoints at both thresholds trace and +1. Where data points were provided at both thresholds, we selected the data point at threshold trace for the overall analysis. Leukocyturia had 5 overall data points with 4 data points at threshold trace and one at +1. CCA POC for *S. haematobium* had 4 overall data points with 2 at threshold trace and 2 at +1.

All studies evaluating CCA POC for *S. mansoni* had reported positivity thresholds; 5 provided data points at both thresholds trace and +1. Where data points were
provided at both thresholds, we selected the data point at threshold trace for the overall analysis. One study (73) introduced substantial heterogeneity because of very extreme estimates of sensitivity (99%) and specificity (19%). We excluded this study from the meta-analysis. The overall analysis therefore contained 11 data points with at threshold ≥trace for which we used the bivariate model for meta-analysis.

### 8.4.5.2 Comparisons of index tests

We compared the accuracy of the reagent strips for microhaematuria with the accuracy of the reagent strips for proteinuria, in detecting *S. haematobium*. These were the only tests with sufficient data to enable comparisons between different types of test. Comparisons between tests were made by adding the covariate test type to the HSROC model, and allowing it to have effect on the accuracy, threshold and shape parameters. We performed indirect comparisons and direct comparisons; in the latter we only included studies that applied both index tests in the same individuals.

### 8.4.5.3 Investigations of heterogeneity

We investigated heterogeneity by examining the forest plots and statistically by including covariates in the HSROC or bivariate model, through subgroup analysis and in sensitivity analysis. In the HSROC model we investigated if these covariates affect the parameters of the HSROC model: accuracy, threshold and shape whereas in the bivariate model we investigated if these covariates affect sensitivity and specificity.

We did not investigate the effect of infection stage and mixed infections because of poor reporting and insufficient data on these items.

We investigated the following sources of heterogeneity: quality of reference standard, positivity threshold, age, gender (proportion of female participation), intensity of infection, prevalence of infection, effect of praziquantel treatment and the QUADAS-2 risk of bias domains. Of these, the covariates gender
(proportion of female participation) and prevalence of infection were analysed as a continuous covariate. The rest were categorical covariates.

We classified studies that used single measurement microscopy (one stool and/or one slide or smear) and those that did not report how the reference standard was conducted as being poor quality reference standards, because single measurements are more likely to miss diseased individuals. We assumed that studies that used multiple measurements of microscopy were likely to report this given the relevance of this additional effort. Reference standards that used multiple urine or stool samples and/or multiple slides or smears were classified as higher quality reference standards.

For the age covariate, there were many mixed adult/children studies that did not state the proportion of adults or children. Some did not state the age of participants. Since accuracy data were not provided for age subgroups in a majority of studies, we dichotomized the age covariate into the groups 'all ages' and 'children only'. We assumed that those that did not state the age had included participants of all ages.

Because the proportion of female and male participants was poorly reported at the test level and at the level of the 2 by 2 tables, we analysed the covariate gender as a continuous variable at the study level. For this covariate, gender was the proportion of female participation. We focused on females because gender may influence accuracy estimates due to factors associated with females such as menstruation and genitourinary tract infections (37,39,74,75).

The WHO recommendations (76) categorises intensity of infection for *S. haematobium* as: (<50eggs/10ml (light) or ≥50eggs/10ml (heavy)) or intensity of *S. mansoni* as (1-99 egg per gram (epg) (Light), 100-399 epg (Moderate), ≥400 epg (Heavy)). In our review, the intensity of infection was reported in different ways (arithmetic mean or range of infection or geometric mean or range of infection or as proportions of participants with light/moderate/heavy infections) and for a majority of included studies not reported at all (63% and 65% for microhaematuria and proteinuria).
respectively). We used the reported estimates of mean (arithmetic/geometric) or median intensity of infection to classify our studies according to the WHO recommendations. We classified studies that reported only proportions of participants with light/moderate/heavy infections or did not report estimates of intensity of infection as unclear.

We examined the effect of treatment with praziquantel on the sensitivity and specificity of the test type microhaematuria because it was the only test with sufficient data to investigate this. Nine studies provided data on praziquantel treatment; 7 were follow up studies with praziquantel given at variable intervals ((1 month)(77), (1 month)(78), (6 weeks)(79), (1 year)(80), (1 year)(81), (1 year)(82), (1 year) (39) and 2 indicated that praziquantel had been given prior to the base line study ((2 years) (83), (2 years)(84)). Where multiple follow up studies were given, we selected data for the first follow up evaluation (39,79). However, pooling results of all studies with varying time intervals would likely introduce a lot of heterogeneity, bias our summary estimates and produce overestimates of sensitivity because studies with long time intervals were likely to have more participants reinfected compared to studies done at shorter time intervals. We opted to present the estimates of sensitivity and specificity of individual studies evaluating the performance of microhaematuria post treatment in ROC space.

We added the following covariates one by one to the HSROC model for microhaematuria and proteinuria and to the bivariate model for CCA POC for S. mansoni: quality of reference standard, age, gender and prevalence of infection. We then performed a subgroup analysis for the covariates, quality of reference standard, age, positivity threshold and intensity of infection for all the 3 index tests.

### 8.4.5.4 Sensitivity analyses

We performed a sensitivity analysis to check robustness of the results when filtration was used as a concentration for urine microscopy for *S. haematobium* and to estimate sensitivity and specificity for the studies with a low risk of bias.
according to the QUADAS domains, patient selection, patient flow and reference standard.

8.5 Results

8.5.1 Results of the search

Our search yielded 17,174 hits. After screening the titles and abstracts, 146 full texts were retrieved and after assessing full texts 86 articles were suitable for inclusion, with 60 excluded. One author we contacted responded for request for information but the data submitted did not meet our eligibility criteria. No extra eligible studies were found through additional searches. This review contains results from 86 articles. The search results can be seen in figure 1.
Circulating antigen tests and urine reagent strips for human schistosomiasis

Figure 1: Flow chart of study inclusion

8.5.1.1 Included studies

Details of included studies can be found in the characteristics of the included studies table. We included 86 studies containing 194,391 patients. Of these
included studies 85 were carried out in Africa and 1 was carried out in South America (Surinam). Only one study was done in a hospital setting (Ante-natal clinic, an outpatient setting). The other tests were done in a field setting (village/school/military camp). *S. haematobium* was evaluated in most studies (n=71) compared to 15 that evaluated *S. mansoni*. One study evaluated both species. Seventy-six studies reported the age of study participants; most of which were conducted in children (n=46, 54%). The median prevalence for *S. haematobium* infection was 42% (Range 21 to 57) and that of *S. mansoni* infection, 44% (Range 27 to 57). The median female participation was 49% (Q1 45, Q3 53) for studies that reported gender (n=62, 72%). A majority of the included studies (n=70, 82%) did not report about the status of praziquantel treatment in the study setting prior to the baseline study. Seventy-seven studies had a cross-sectional design; 6 were cohort studies (longitudinal studies with follow up) and 3 were case control studies with controls from the same population (nested case-control studies). We included 80 English studies and 6 French studies. One study (49) retrieved through an updated search contained recent data for studies retrieved previously (85–87). In this case we used data for the 2 by 2 tables from the most recent publication (49)

### 8.5.1.2 Excluded studies

We excluded 60 articles after full text reading. We excluded 17 case-control studies with healthy controls or with controls from non-endemic areas of schistosomiasis. We could not extract data from 2 by 2 tables from 16 studies. Eleven studies were not test accuracy studies and 4 studies only enrolled proven cases of schistosomiasis. Six studies used other reference standards than microscopy, 3 studies used other index tests to diagnose schistosomiasis, which did not fulfill our inclusion criteria and 3 studies had tests similar tests done on the same population as other already included studies.

### 8.5.2 Methodological quality of included studies

Figure 2 shows the results of the quality appraisal of the 86 included studies. Using the QUADAS-2 tool we evaluated the studies for risk of bias in the
domains: patient selection, index test, reference standard and patient flow. In general, poor reporting of quality items hindered our evaluation of quality. We therefore rated the risk of bias for the domains largely as unclear. In the patient selection domain, about 75% of studies were rated as having an unclear risk of bias. For index tests, unclear risk of bias ranged from 75% to about 98% (About 98% for reagent strip for microhaematuria, about 95% for reagent strip for proteinuria and about 75% for CCA POC test). None of the studies had a high risk of bias in the index test domain. For the reference standard, 50% of the studies had a high risk of bias whereas the other half had an unclear risk of bias. For the patient flow domain about 75% of the studies had a low risk of bias with the remaining studies having an unclear risk. The concerns for applicability for all four domains were predominantly low.

Figure 2: Assessment of risk of bias and concerns for applicability

8.5.3 Accuracy results

A summary of the main findings can be found in the summary of findings table. Below we present in detail the overall findings for the index tests for which we performed a meta-analysis.
1. Urine reagent strips

*For Microhaematuria*

There were 70 evaluations of the reagent strip for microhaematuria with a total of 100,839 individuals. All evaluations were conducted in Africa. The median prevalence of *S. haematobium* was 44% (range 8% to 87%) and the median female participation was 49% (Q1 44, Q3 53). A majority of these evaluations were conducted with a poor quality reference standard of only one slide/person (n=60, 86%) and most evaluations were carried out in mixed populations of adults and children (n=40, 57%). These evaluations were from articles published between the years 1979 and 2012 with a large proportion (n=43, 62%) published between 1979 and 1999. Most evaluations (n=25, 36%) were done with the brand from the manufacturer Ames.

The forest plot and SROC curve for the reagent strip for microhaematuria reveals heterogeneity for both estimates of sensitivity and specificity (Fig 3, Fig 4)

The meta-analytical sensitivity and specificity (95% Confidence interval (CI)) of data at mixed thresholds were 76% [72 % to 80%] and 86% [83% to 89%]
Circulating antigen tests and urine reagent strips for human schistosomiasis

Figure 3: Forest plot of sensitivity and specificity for microhaematuria
Figure 4: SROC plot of sensitivity of sensitivity and specificity for microhaematuria

For Proteinuria

There were 43 evaluations of the reagent strip for proteinuria with a total of 81,201 individuals. All evaluations were conducted in Africa. The median prevalence of *S. haematobium* was 51% (range 4% to 89%) and the median female participation was 49% (Q1 45, Q3 53). A majority of these evaluations were conducted with a poor quality reference standard (n=34, 79%) and most evaluations were carried out in mixed populations of adults and children (n=28, 65%). These evaluations were from articles published between the years 1979 and 2012, with the largest proportion (n=27, 64%) published before the year
Circulating antigen tests and urine reagent strips for human schistosomiasis

2000. Most evaluations (n=17, 39%) were done with the brand from the manufacturer Ames.

The forest plot (Fig 5) and SROC plot (Fig 6) for the reagent strip for proteinuria reveals more heterogeneity for estimates of sensitivity than specificity. The meta-analytical sensitivity and specificity (95% CI) of data at mixed thresholds were 61% [53% to 69%] and 83% [79% to 88%].

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**Figure 5:** Forest plot of sensitivity and specificity for proteinuria
Figure 6: SROC plot of sensitivity and specificity for proteinuria

For Leukocyturia

There were 5 evaluations of the reagent strip for leukocyturia (with data from 4 publications with a total of 1532 individuals). Of these evaluations, 2 were carried out with a higher quality reference standard (67%). The median prevalence of *S. haematobium* was 34% (range 4% to 77%) and the median female participation was 100% (Q1 68, Q3 100). All evaluations except one were conducted in Africa in mixed populations of adults and children. These evaluations were from articles published between the years 1992 and 2000, with the majority (n=3) published before the year 2000. Two different test brands
were evaluated. Most evaluations (n=3,60%) were done with the Nephur test from Boehringer Mannheim.

The forest plot (Fig 7) and SROC plot (Fig 8) for the reagent strip for proteinuria reveals more heterogeneity for estimates of specificity than sensitivity. The ROC plot also reveals a poor accuracy of the test as most study points lie close to the diagonal line. The meta-analytical sensitivity and specificity (95% CI) of data at mixed thresholds were 58% [44% to 71%] and 61% [34% to 88%].

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdel-Wahhab 1992</td>
<td>46</td>
<td>20</td>
<td>96</td>
<td>260</td>
<td>0.32 [0.25, 0.41]</td>
<td>0.93 [0.89, 0.96]</td>
</tr>
<tr>
<td>Gundersein 1996</td>
<td>37</td>
<td>160</td>
<td>14</td>
<td>49</td>
<td>0.73 [0.58, 0.84]</td>
<td>0.23 [0.18, 0.30]</td>
</tr>
<tr>
<td>Poggensee 2000_settingA</td>
<td>4</td>
<td>92</td>
<td>3</td>
<td>76</td>
<td>0.57 [0.48, 0.69]</td>
<td>0.45 [0.38, 0.53]</td>
</tr>
<tr>
<td>Poggensee 2000_settingB</td>
<td>38</td>
<td>32</td>
<td>29</td>
<td>29</td>
<td>0.57 [0.44, 0.69]</td>
<td>0.48 [0.35, 0.61]</td>
</tr>
<tr>
<td>Rasendramino 1998</td>
<td>238</td>
<td>30</td>
<td>182</td>
<td>57</td>
<td>0.57 [0.52, 0.61]</td>
<td>0.76 [0.68, 0.83]</td>
</tr>
</tbody>
</table>

**Figure 7:** Forest plot of sensitivity and specificity for Leukocyturia

**Figure 8:** SROC plot for sensitivity and specificity for Leukocyturia
Urine CCA POC test

For *S. haematobium*

There were 4 evaluations of the CCA POC test for *S. haematobium* (based on data from 4 publications with a total population of 901 individuals). The median prevalence of *S. haematobium* was 40% (range 31% to 48%) and the median female participation was 47% (Q1 40, Q3 51). A majority of these evaluations were conducted with a poor quality reference standard (n=3, 75%). All evaluations were conducted in Africa. All evaluations contained data from children only. These evaluations were from articles published between the years 2008 and 2011. Four different test brands were evaluated.

The Forest (Fig 9) and ROC plots (Fig 10) for this test reveals a high degree of heterogeneity for both estimates of sensitivity and specificity. The ROC plot also reveals a poor accuracy of the test as the study points lie close to the diagonal line. The meta-analytical sensitivity and specificity (95% CI) of data at mixed thresholds were 39% [6% to 73%] and 78% [55% to 100%].

**Figure 9:** Forest plot of sensitivity and specificity for CCA-POC test for *S. haematobium*
Circulating antigen tests and urine reagent strips for human schistosomiasis

Figure 10: SROC plot of sensitivity and specificity for CCA-POC test for *S. haematobium*

For *S. mansoni*

There were 11 evaluations of the CCA POC test for *S. mansoni* (based on data from 11 publications with a total population of 5420 individuals). The median prevalence of *S. mansoni* was 60% (range 50% to 75%) and the median female participation was 49% (Q1 45, Q3 50). A majority of these evaluations were conducted with a poor quality reference standard (n=9, 82%). All evaluations were conducted in Africa and all evaluations except one contained data from children only. These 11 evaluations were from articles published between the years 2007 and 2013. Two different test brands were evaluated: Rapid diagnostic tests from Pretoria South Africa and Schistosomiasis one step test from EVL Holland. Most evaluations (n=8) were done with the Rapid diagnostic test from South Africa.

One study (73) introduced substantial heterogeneity because of very extreme estimates of sensitivity (99%) and specificity (19%) for CCA POC for *S. mansoni*. We excluded this study from the meta-analysis.
Chapter 8

The forest plot for this test reveals more heterogeneity for estimates of specificity compared to estimates of sensitivity (Fig 11). The meta-analytical sensitivity and specificity (95% CI) of data at a threshold of ≥ trace positive were 87% [85% to 90%] and 61% [51% to 70%] (Fig 12).

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashton 2011</td>
<td>64</td>
<td>53</td>
<td>8</td>
<td>151</td>
<td>0.86 [0.79, 0.90]</td>
<td>0.74 [0.67, 0.80]</td>
</tr>
<tr>
<td>Coiley 2013_Uganda</td>
<td>114</td>
<td>199</td>
<td>11</td>
<td>176</td>
<td>0.91 [0.85, 0.96]</td>
<td>0.47 [0.42, 0.52]</td>
</tr>
<tr>
<td>Coilibay 2013_Coiley</td>
<td>278</td>
<td>42</td>
<td>38</td>
<td>249</td>
<td>0.89 [0.84, 0.94]</td>
<td>0.84 [0.81, 0.89]</td>
</tr>
<tr>
<td>Erko 2013_Coiley</td>
<td>366</td>
<td>103</td>
<td>23</td>
<td>166</td>
<td>0.83 [0.76, 0.90]</td>
<td>0.65 [0.59, 0.70]</td>
</tr>
<tr>
<td>Legesse 2007</td>
<td>136</td>
<td>59</td>
<td>21</td>
<td>41</td>
<td>0.86 [0.80, 0.91]</td>
<td>0.41 [0.31, 0.51]</td>
</tr>
<tr>
<td>Legesse 2008</td>
<td>56</td>
<td>65</td>
<td>12</td>
<td>52</td>
<td>0.85 [0.71, 0.90]</td>
<td>0.44 [0.35, 0.54]</td>
</tr>
<tr>
<td>Navaratnam 2012</td>
<td>149</td>
<td>181</td>
<td>34</td>
<td>205</td>
<td>0.81 [0.75, 0.87]</td>
<td>0.53 [0.48, 0.58]</td>
</tr>
<tr>
<td>Shane 2011_Coiley</td>
<td>233</td>
<td>664</td>
<td>30</td>
<td>833</td>
<td>0.87 [0.82, 0.91]</td>
<td>0.50 [0.43, 0.58]</td>
</tr>
<tr>
<td>Stichard 2006</td>
<td>116</td>
<td>25</td>
<td>24</td>
<td>105</td>
<td>0.80 [0.76, 0.89]</td>
<td>0.81 [0.73, 0.87]</td>
</tr>
<tr>
<td>Tchenu 2012_Coiley</td>
<td>41</td>
<td>31</td>
<td>9</td>
<td>57</td>
<td>0.82 [0.72, 0.91]</td>
<td>0.65 [0.54, 0.75]</td>
</tr>
</tbody>
</table>

**Figure 11:** Forest plot of sensitivity and specificity for CCA POC test for *S. mansoni*

**Figure 12:** SROC plot of sensitivity and specificity for CCA POC test for *S. mansoni*
2. Comparisons of accuracy between reagent strip for microhaematuria and proteinuria

The results of the comparisons between microhaematuria and proteinuria are outlined in the summary of findings table. There was no statistically significant difference between the accuracy of microhaematuria and that of proteinuria when the tests were compared in different populations using all studies (indirect comparisons, p=0.21)(fig 13). This can be demonstrated in the ROC curve showing the curves of the tests being close together and crossing. The difference in accuracy was also not statistically significant when the tests were directly compared in the same individuals (p=0.17). There was a statistically significant difference in the threshold parameter when the tests were compared in different populations using all studies (p=0.004) and when the tests were directly compared in the same individuals (p=0.003). This could imply that one test has another operating threshold than the other and though overall accuracy is not statistically different, sensitivity and specificity may be different under field circumstances.

Figure 13: SROC plot showing indirect comparisons between microhaematuria and proteinuria
3. Investigations of heterogeneity

Covariates in the models

The covariates quality of reference standard, age, gender (% female participation), prevalence of infection and intensity of infection were added to the HSROC model. We investigated if these covariates affect the parameters of the HSROC model: accuracy, threshold and shape.

For the reagent strip for microhaematuria, the covariates age (p=0.004) and gender (% female participation) (p=0.003) had statistically significant effects on the threshold parameter of the HSROC model.

For the reagent strip for proteinuria, no covariate had a statistically significant effect on the parameters of the HSROC model.

For CCA POC to detect *S. mansoni*, only quality of reference standard had a statistically significant effect on sensitivity (p=0.0011). Sensitivity was higher with the better reference standard.

We did not see any significant effects of gender and prevalence of infection on the accuracy estimates of any of the index tests.

Subgroup analysis

Tables 1-3 outline the results of subgroup analysis on the tests microhaematuria, proteinuria and CCA POC for *S. mansoni*. When the tests were evaluated against the higher quality reference standard (i.e. when multiple samples were analysed), the sensitivity was lower for microhaematuria (69 % vs. 76%) and proteinuria (47% vs. 63%) in comparison to a poor quality reference standard. The specificity of these tests was comparable. In contrast, the sensitivity and specificity of CCA POC for *S. mansoni* were both higher (88% vs. 86% and 69% vs. 62% respectively) when measured against a higher quality reference standard in comparison to a poor quality reference standard.
Microhaematuria and proteinuria had a higher sensitivity (78% vs. 73% & 68% vs. 56%) in children compared to mixed populations of adults and children. The specificity was higher for microhaematuria (91% vs. 82%) but specificity comparable for proteinuria (83% vs. 82%) in children compared to mixed populations of adults and children. All except one study for CCA POC for *S. mansoni* were carried out with children. At a positivity threshold of ≥ 1, the sensitivity of CCA POC for *S. mansoni* was lower (72% vs. 87%) and specificity higher (85% vs. 61%) than at a positivity threshold of trace positive. In the light intensity subgroup the sensitivity was slightly lower for microhaematuria (73% vs. 76%) and the specificity was slightly higher (88% vs 86%) compared to results of the overall analysis. In contrast, the sensitivity (60% vs. 61%) and specificity (83% vs 83%) for proteinuria were comparable. There was insufficient data to estimate the sensitivity and specificity of CCA POC for *S. mansoni* in light intensity settings.

The forest plot (Fig 14) demonstrating sensitivity and specificity for microhaematuria after praziquantel treatment shows a lot of variation of the estimates (predominantly for sensitivity) of the individual studies.

**Figure 14:** Forest plot of sensitivity and specificity for microhaematuria after treatment with praziquantel

**Sensitivity analysis**

For microhaematuria, when the analysis was limited to studies that used filtration only as the concentration method for urine microscopy, the sensitivity (73% [69%-78%] vs. 76% [72%-80%]) was lower and specificity were comparable (86% [82%-89%] vs. 86% [82%-89%]) to that produced by the overall analysis. For proteinuria, when the analysis was limited to studies that
used filtration only as the concentration method for urine microscopy the sensitivity was comparable (62% [52%-71%] vs. 61% [53%-69%]) and specificity (80% [73%-86%]) was lower than that produced by the overall analysis (83% [77%-88%]) (Tables 1-3).

The sensitivities and specificities of microhaematuria, were comparable when limited to the studies with a low risk of bias for the patient flow domain. The sensitivity of proteinuria was higher when limited to the studies with a low risk of bias for the patient selection domain (64%) and patient flow domain (67%). The specificity on the other hand was comparable for these two domains. The sensitivity and specificity of CCA POC for *S. mansonii* were comparable when limited to the studies with a low risk of bias for the patient flow domain (Tables 1-3). There was insufficient data to estimate the sensitivity and specificity for studies with a low risk of bias in the other domains; reference standard and patient selection, for the CCA POC test.

### Table 1. Subgroup & Sensitivity Analyses of Urine Reagent strip for Microhaematuria

<table>
<thead>
<tr>
<th>Group</th>
<th>Covariate</th>
<th>Subgroup</th>
<th>n (N=70)</th>
<th>Sensitivity [95% CI]</th>
<th>Specificity [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td>0.76 [0.72-0.80]</td>
<td>0.86 [0.83-0.89]</td>
</tr>
<tr>
<td>Subgroup analysis</td>
<td>Reference Standard</td>
<td>Higher quality (&gt;1 sample)</td>
<td>10</td>
<td>0.71 [0.62-0.80]</td>
<td>0.85 [0.78-0.93]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor quality (1 sample)</td>
<td>60</td>
<td>0.76 [0.72-0.81]</td>
<td>0.86 [0.83-0.90]</td>
</tr>
<tr>
<td></td>
<td>Threshold</td>
<td>≥+1</td>
<td>23</td>
<td>0.78 [0.72-0.85]</td>
<td>0.85 [0.79-0.91]</td>
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<tr>
<td></td>
<td>Age</td>
<td>Children only</td>
<td>30</td>
<td>0.78 [0.72-0.84]</td>
<td>0.91 [0.88-0.94]</td>
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<tr>
<td></td>
<td>Intensity of infection</td>
<td>Light</td>
<td>28</td>
<td>0.73 [0.66-0.79]</td>
<td>0.88 [0.84-0.92]</td>
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<tr>
<td>Sensitivity analysis</td>
<td>Concentration</td>
<td>Filtration only</td>
<td>62</td>
<td>0.73 [0.69-0.78]</td>
<td>0.86 [0.82-0.89]</td>
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<tr>
<td></td>
<td>QUADAS Patient selection</td>
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<td>16</td>
<td>0.78 [0.70-0.86]</td>
<td>0.86 [0.79-0.92]</td>
</tr>
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<td>Low risk of bias</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>QUADAS Flow &amp; Timing</td>
<td>Low risk of bias</td>
<td>49</td>
<td>0.78 [0.73-0.82]</td>
<td>0.86 [0.82-0.90]</td>
</tr>
</tbody>
</table>

* Insufficient data to synthesize
### Table 2. Subgroup & Sensitivity Analyses of Urine Reagent strip for Proteinuria

<table>
<thead>
<tr>
<th>Group</th>
<th>Covariate</th>
<th>Subgroup</th>
<th>n (N=43)</th>
<th>Sensitivity [95% CI]</th>
<th>Specificity [95% CI]</th>
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<tbody>
<tr>
<td>Overall</td>
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<td></td>
<td>0.61 [0.53-0.69]</td>
<td>0.83 [0.77-0.88]</td>
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<tr>
<td><strong>Subgroup analysis</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference standard</td>
<td></td>
<td>Higher quality (&gt;1 sample)</td>
<td>9</td>
<td>0.49 [0.28-0.70]</td>
<td>0.83 [0.76-0.90]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor quality (1 sample)</td>
<td>34</td>
<td>0.63 [0.54-0.71]</td>
<td>0.84 [0.77-0.90]</td>
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<tr>
<td>Threshold</td>
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<td>≥+1</td>
<td>13</td>
<td>0.65 [0.51-0.79]</td>
<td>0.77 [0.61-0.94]</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>Children only</td>
<td>15</td>
<td>0.68 [0.57-0.79]</td>
<td>0.83 [0.76-0.89]</td>
</tr>
<tr>
<td>Intensity of infection</td>
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<td>Light</td>
<td>15</td>
<td>0.60 [0.43-0.77]</td>
<td>0.83 [0.73-0.93]</td>
</tr>
<tr>
<td><strong>Sensitivity analysis</strong></td>
<td>Concentration</td>
<td>Filtration only</td>
<td>35</td>
<td>0.62 [0.52-0.71]</td>
<td>0.80 [0.73-0.86]</td>
</tr>
<tr>
<td></td>
<td>QUADAS Patient selection</td>
<td>Low risk of bias</td>
<td>11</td>
<td>0.64 [0.50-0.79]</td>
<td>0.81 [0.70-0.93]</td>
</tr>
<tr>
<td></td>
<td>QUADAS Reference Standard</td>
<td>Low risk of bias*</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>QUADAS Flow &amp; Timing</td>
<td>Low risk of bias</td>
<td>33</td>
<td>0.67 [0.59-0.76]</td>
<td>0.82 [0.73-0.88]</td>
</tr>
</tbody>
</table>

* Insufficient data to synthesize

### Table 3. Subgroup & Sensitivity Analyses for CCA POC test for *S. mansoni*

<table>
<thead>
<tr>
<th>Group</th>
<th>Covariate</th>
<th>Subgroup</th>
<th>n(N=11)</th>
<th>Sensitivity [95% CI]</th>
<th>Specificity [95% CI]</th>
</tr>
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<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td>0.87 [0.85-0.90]</td>
<td>0.61 [0.51-0.70]</td>
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<tr>
<td><strong>Subgroup analysis</strong></td>
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<td></td>
</tr>
<tr>
<td>Reference standard</td>
<td></td>
<td>Higher quality (&gt;1KK)</td>
<td>41</td>
<td>0.88 [0.82-0.94]</td>
<td>0.69 [0.48-0.90]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor quality (1KK)</td>
<td>9</td>
<td>0.86 [0.84-0.88]</td>
<td>0.62 [0.52-0.72]</td>
</tr>
<tr>
<td>Positivity Threshold</td>
<td></td>
<td>&gt; +1</td>
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<td>0.72 [0.62-0.83]</td>
<td>0.85 [0.74-0.96]</td>
</tr>
<tr>
<td>Intensity of infection</td>
<td></td>
<td>Low*</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Sensitivity analysis</strong></td>
<td>Age</td>
<td>Children</td>
<td>10</td>
<td>0.87 [0.85-0.90]</td>
<td>0.63 [0.53-0.72]</td>
</tr>
<tr>
<td></td>
<td>QUADAS Patient selection</td>
<td>Low risk of bias*</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>QUADAS Reference Standard</td>
<td>Low risk of bias*</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>QUADAS Flow &amp; Timing</td>
<td>Low risk of bias</td>
<td>8</td>
<td>0.86 [0.83-0.89]</td>
<td>0.60 [0.51-0.70]</td>
</tr>
</tbody>
</table>

1Two studies had data points are both trace and +1.

*Insufficient data to synthesize
8.6 Discussion

8.6.1 Summary of main results

This review focused on analysing the accuracy of urine reagent strips for the diagnosis of *S. haematobium* and circulating antigen tests for the detection of *S. haematobium* and *S. mansoni* infections. Microscopy was used as the reference standard and there were 86 studies which fitted our inclusion criteria, and whose data were therefore used in this review. The main results including the average sensitivities and specificities for tests included in the meta-analyses are reported in the summary of findings table.

Most of the studies included in our overall meta-analyses used a ‘poor quality reference test’: microhaematuria (81%), proteinuria (73%), leukocyturia (60%), CCA POC for *S. haematobium* (75%) and CCA POC for *S. mansoni* (81%). This implies that infections missed by single sample microscopy may have increased the number of false positives identified by the index tests, consequently leading to lower estimates of specificity.

Our overall analyses suggest that among the tests used to detect *S. haematobium*, the urine reagent strip for microhaematuria detects the largest proportion of schistosome infections, identified by microscopy (sensitivity, 76%) and also detects a largest proportion of non-infections identified by microscopy (specificity, 86%). Proteinuria follows suit with a sensitivity of 61% and specificity of 83%.

The superior performance of microhaematuria over proteinuria was not statistically significant when the comparison was performed both indirectly (using all studies) and directly (using paired studies) within the HSROC model. When compared against a higher quality reference standard (multiple measurements), both microhaematuria and proteinuria had a lower sensitivity of 71% and 49% respectively but a comparable specificity.

Our results suggest that the urine reagent strip to detect leukocyturia is limited by low sensitivity (58%) and specificity (61%) and is not useful in practice. The
CCA POC test has a very low sensitivity (39%) to detect *S. haematobium*, and a specificity of 78% and may not be suitable for mapping or estimation of infection because it misses very many infections identified by microscopy.

The CCA POC test for *S. mansoni* detected a large proportion of infections identified by microscopy (sensitivity, 87%). However, it also detected a proportion of the non-infected cases identified by microscopy (specificity, 61%). The low specificity can be explained by the fact that most studies in the overall analyses were measured against a poor quality reference standard. When compared against a higher quality reference standard, the CCA POC test had a comparable sensitivity (88%) but higher specificity (69%). Arguably, if the reference standard was even better then this specificity might have increased further.

Due to insufficient studies we were unable to generate summary estimates for the circulating antigen ELISA tests (CCA & CAA). The estimates of sensitivity and specificity from the included studies evaluating these tests ranged widely. The results of our assessment of risk of bias of the included studies were largely unclear due to poor reporting of items in the studies.

**8.6.2 Application of the meta-analysis to a hypothetical cohort**

The summary of findings table applies the results of the meta-analyses to a hypothetical cohort of 1000 individuals suspected of having active *S. haematobium* and/or active *S. mansoni* infection in a field setting. We illustrate the impact of using microhaematuria, proteinuria, leucocyturia and CCA POC for *S. haematobium* in a setting with a prevalence of *S. haematobium* infection of 42% and the impact of using CCA POC for *S. mansoni* in a setting with a prevalence of *S. mansoni* infection 44%. These are the estimates of median prevalence of infection obtained from all the included studies in this review.

**8.6.2.1 S. haematobium infection**
If the point estimates of the tests for *S. haematobium* are applied to a hypothetical cohort of 1000 individuals suspected of having active *S. haematobium* infection, where 420 actually have the infection, then the strip for microhaematuria would be expected to miss (81) and falsely diagnose (101) the least number of cases.

For the other tests (in increasing order of missed cases); the strip for proteinuria would be expected to miss 164 cases and falsely diagnose 99 cases. Leukocyturia would be expected to miss 176 cases and falsely diagnose 226 cases and CCA POC test would be expected to miss 256 cases and falsely diagnose 128 cases.

Proteinuria would be expected to miss 64% more cases than microhaematuria and falsely diagnose 22% more cases than microhaematuria.

Overall, when mapping infection, the prevalence of microhaematuria would seem to be 40%, close to the true prevalence of 42%. The prevalence of proteinuria would seem to be 35%, that of leukocyturia 47% and that of CCA POC, 29%. In case of mass-treatment, the ultimate consequences of these numbers would depend on the minimal prevalence needed to start mass-treatment.

### 8.6.2.2 *S. mansoni* infection

If the point estimates for CCA POC test are applied to the same hypothetical cohort of 1000 patients suspected of having active *S. mansoni* infection, where 440 actually have the infection, then CCA POC would be expected to miss 57 cases and falsely diagnose 218 cases. This would result in an observed prevalence of 60% when mapping infection...

### 8.6.3 Comparison with other reports

The absence of a suitable gold standard for active schistosomiasis is reflected in the existing literature where different reference standards are used with subsequent variation in accuracy (especially with specificity) of the index test (49,85,87–93).
A meta-analysis was recently published that assessed the accuracy of urine reagent strips for microhaematuria against conventional microscopy as a reference standard (88). Unlike King’s review, our review also estimated the accuracy of other urine reagent strips, for proteinuria and leukocyturia. In order to guide decision making, it is important to show which of these tests fairs better. In our case, our analyses suggest that microhaematuria has a higher sensitivity than proteinuria and leukocyturia.

Compared to results from King’s meta-analysis (88), our estimate of sensitivity for microhaematuria was lower (76% vs. 81%) but specificity comparable (86% vs. 89%). This difference may be attributed to the method of meta-analysis used. King used the HSROC regression following a Bayesian Monte Carlo Markov chain approach (94) while we used the HSROC model recommended in the Cochrane handbook (70). With regard to sources of heterogeneity, some of our results are also comparable to that of King and Bertsch (88). For instance, King found through multivariable regression modelling that the urine heme dipstick had a better performance in children compared to when done in mixed populations of adults and children (rDOR =3.16). In our review, we also found that the sensitivity and specificity was higher in studies on children compared to studies on mixed population of adults and children. We strongly confirm that this test is therefore highly suitable for mass mapping of school aged children in endemic areas. Again our analyses also demonstrated that the sensitivity of the urine heme dipstick was lower in settings of low intensity (72%) compared to that of the overall estimate (75%). This finding was similar to King’s, which demonstrated that the sensitivity of the urine heme dipstick was lower in settings of lower infection intensity (65%) in the subgroup analysis compared to the overall analysis (81%). However it should be noted that our definition of light intensity differed from that of King. We selected the more commonly used WHO recommended cutoff of <50 eggs per 10ml whereas King defined low intensity as ≤100 eggs/10ml. This could in part explain why our sensitivity estimates were higher than King’s in settings of light intensity.

A key difference between our review and that of King concerned the effect of treatment on the estimate of sensitivity of the heme dipstick. In a subgroup of 8
studies with mixed post treatment evaluations of 1 year (n=6), 6 months (n=1) and 1 month (n=1), King’s review produced a lower summary estimate of sensitivity (72%) in the subgroup of treated populations as compared to the overall analysis (81%). King considered treatment evaluations with praziquantel and metrifonate whereas we focused on studies that evaluated the effect of praziquantel treatment as this is the current drug of choice. Due to studies with varied time intervals between treatment and retesting, we opted not to pool the estimates of the studies as this would likely produce biased overestimates of sensitivity and specificity. Studies with long time intervals were likely to have more participants reinfected compared to studies carried out at shorter time intervals, as well as potentially being confounded by repeated treatments by country programmes.

A recently published multi-centre evaluation of CCA POC tests done in five African countries (49) recommended the CCA POC test for *S. mansoni* (evaluated with a positivity threshold of ≥trace positive) as a sufficiently sensitive and specific tool for mapping intestinal schistosomiasis in moderate to high prevalence areas and therefore as a viable alternative to microscopy (92). Acknowledging the absence of a gold standard, this multi-centre study used latent class analysis (modeling results from CCA POC, Kato Katz and PCR) to generate an overall estimate of 86% sensitivity and 72% specificity of CCA POC based on data from 4405 school age children. Using microscopy only (KK) as the reference standard, our review, which incorporated all of their results with additional studies, produced a comparable summary estimate of 87% sensitivity but a lower summary estimate of 61% specificity at a threshold of trace positive. The differences in specificity could be explained by the reference standard and indicates that some of the false positives identified by CCA POC, are indeed likely to be true infections, which are not detected by standard microscopy.

Few studies exist that fully evaluate the accuracy of the circulating antigen ELISA tests (CCA & CAA). The serum CAA ELISA test is currently being developed into a point of care format for *S. mansoni* (95) and *S. haematobium* (96) with promising results of analytical sensitivity and specificity. In our review, the sensitivity of the included studies evaluating the serum CAA ELISA test for *S.
Circulating antigen tests and urine reagent strips for human schistosomiasis

*mansoni* ranged widely from 47%-94% and specificity ranged widely from 8% to 100%. The sensitivity of the included studies evaluating serum CAA ELISA test for *S. haematobium* ranged from 55%-97% and specificity was low and ranged from 24 % to 57%. However, the studies included in our review were carried out before the year 2000 with in-house tests. The tests currently being developed are most likely improved versions and therefore more current studies analysing the clinical sensitivity and specificity of the serum ELISA tests are needed to conclusively know if they are suitable for the diagnosis of active schistosomiasis.

8.6.4 Strengths and limitations of the review

8.6.4.1 Strengths

We have evaluated the accuracy of POC tests currently being used and also tests that have recently transformed into POC tests for detection of active schistosomiasis in endemic areas. This makes our review relevant to current practice. To avoid missing studies we did not use a search filter and we did not limit our search by publication year or language and to limit bias, two people performed data extraction independently.

8.6.4.2 Weaknesses

a. Choice of the reference standard

In light of the absence of a suitable gold standard for active schistosomiasis and the presence of other proposed alternative reference standards, evaluating index tests with only microscopy as the reference standard may be considered a shortcoming of our review. However because microscopy remains the most commonly used test and therefore reference test, we wanted our review to be applicable to current practice. Our review gives a better insight on the proportion of cases detected and proportion of cases misclassified by urine reagent strips and CCA POC tests when microscopy is used as the reference standard. A more reliable way of evaluating if an index test can replace microscopy would be to compare the accuracy of microscopy, urine reagent strips and circulating antigen tests against other proposed reference standards in the same set of participants (direct comparison studies). A few studies have
compared the accuracies of one or more KK smears and CCA-POC against a reference standard comprising six or more KK smears (85,87,90) or against PCR as the reference test (92). All these studies have shown CCA POC test to be more sensitive but less specific than single or double KK. More direct comparative studies and reviews are needed to reliably confirm this finding and identify sources of variation in results.

b. Quality of included studies

Poor and inconsistent reporting of patient characteristics such as clinical status of participants, intensity of infection, administration of praziquantel treatment and the conduct of the study limited our investigations of sources of heterogeneity and risk of bias assessment.

In our review, the reporting of intensity of infection was unclear (reported in different ways (arithmetic mean or range of infection or geometric mean or range of infection or proportions with light/moderate/heavy infections) or not reported at all) for a large proportion of the included studies (Microhaematuria (44%), Proteinuria (42%) and CCA POC (45%). It was therefore difficult to effectively investigate its influence on the accuracy of the evaluated tests. It was also a challenge to fully investigate the effect of praziquantel treatment on the accuracy of the evaluated tests because 82% of the studies did not report the treatment status of the participants prior to the study. The effect of intensity of infection and effect of praziquantel treatment on the accuracy of diagnostic tests for schistosomiasis is currently an important concern for national control programmes, particularly as praziquantel treatments progress, with subsequent decreases in infection intensities. Indeed, in areas where the force of infection and associated morbidity has been greatly reduced, some programmes are beginning to focus on elimination, it is therefore of vital importance that highly sensitive tests are used for monitoring, and that highly sensitive and specific tests are used in efficacy studies pre and post treatment.8.6.5 Applicability of findings to the review question
Our concern about the applicability of the included studies to our review question was low as assessed by QUADAS-2. As all but one study were carried out in Africa and all but one study were done in field settings making our results highly applicable for use in endemic communities where disease control programs are often targeted. However, one area that may limit the applicability of our findings to the review question is our investigations into the sources of heterogeneity such as effect of praziquantel treatment and risk of bias assessment on the accuracy estimates of the evaluated tests. As discussed earlier, poor and inconsistent reporting limited this investigation. In light of the ongoing disease control programs it would be useful to policy makers to fully show any variation of test accuracy with effect of praziquantel treatment. Knowing the risk of bias of included studies would also help in objectively assessing the strength of the evidence. Authors are therefore encouraged to use the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines (97) in reporting the design and conduct of their studies.

8.7 Authors’ conclusions

8.7.1 Implications for practice

Among the evaluated tests for *S. haematobium* infection, microhaematuria detected the largest proportion of infections and non-infections identified by microscopy. This test could continue to serve as a replacement test for microscopy for initial mapping or estimation of *S. haematobium* infection, particularly in endemic areas with a moderate to high prevalence of infection.

The CCA POC test for *S. mansoni* detects a very large proportion of infections identified by microscopy but misclassifies many microscopy negatives as positives in endemic areas with a moderate to high prevalence of infection. This may be because the test is potentially more sensitive than microscopy. Nevertheless, health workers should interpret the results with care, when using the test for initial mapping or estimation of *S. mansoni* infection, as some of the positives may still be false positives.
Besides the accuracy of a test the choice of a suitable diagnostic test should be made in light of cost and logistical considerations. Costs for microscopy (US$ per examination, 0.3 for a single thick KK smear) (26), and the reagent strips for microhaematuria (US$ 0.32) (98) are comparable but the strips are easier to use and interpret and are therefore not logistically challenging in field settings. The CCA POC tests are more costly (US$ 2.6 per examination) (26), but are still rapid and easy to use and interpret, highly portable and require less technical personnel than microscopy and are therefore also suitable for field screening and diagnosis.

8.7.2 Implications for research

As control programmes progress with expected subsequent decrease in prevalence and intensity of infection, we highlight the importance of more primary research identifying a suitable clinical reference standard for active schistosomiasis.

Additional studies comparing the accuracy of microscopy, circulating antigen tests and urine reagent strips to other proposed reference standards are needed to reliably recommend a suitable replacement for microscopy in practice.

Further studies to identify other sensitive tests to detect active *S. haematobium* and *S. mansoni* infections and further evaluations of the CAA test as a future POC test for serum or urine are also needed.

To reliably recommend suitable tests for monitoring effects of praziquantel treatment in disease control programs more follow up studies are required to evaluate the effects of praziquantel treatment on the intensity of infection and accuracy of urine reagent strips and circulating antigen tests.

Further research on cost effectiveness of diagnostic tests in areas of different endemicity is also needed as cost is a key deciding factor in resource limited settings.
Finally authors of primary test accuracy studies need to be encouraged to use the STARD guidelines in reporting the design and conduct of their studies. This will enable systematic reviewers to better synthesize the data and draw conclusions on the risk of bias in studies of test accuracy.

**Summary of findings table for tests to detect S. haematobium**

<table>
<thead>
<tr>
<th>What is the diagnostic accuracy of circulating antigen tests and biochemical urine reagent strips for <em>S. haematobium</em> infection?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients/Population</td>
</tr>
<tr>
<td>Prior treatment with praziquantel before baseline study</td>
</tr>
<tr>
<td>Prior testing</td>
</tr>
<tr>
<td>Settings</td>
</tr>
<tr>
<td>Index tests</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Reference standard</td>
</tr>
<tr>
<td>Importance</td>
</tr>
<tr>
<td>Studies</td>
</tr>
<tr>
<td>Quality concerns</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test types</th>
<th>No. of evaluation s</th>
<th>Average pooled results (95% random effects CI)</th>
<th>Consequences in a cohort of 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>True prevalence of <em>S. haematobium</em></td>
<td>Missed cases (FN)</td>
</tr>
</tbody>
</table>
### Biochemical Urine reagent strips

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value</th>
<th>Number of Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>For microhaematuria</td>
<td>76 % (72% to 80%)</td>
<td>86 % (83% to 89%)</td>
<td>101</td>
<td>420 infected people in a population of 1000</td>
</tr>
<tr>
<td>For proteinuria</td>
<td>61 % (53% to 69%)</td>
<td>83 % (77% to 88%)</td>
<td>164</td>
<td>420 infected people in a population of 1000</td>
</tr>
<tr>
<td>For leukocyturia</td>
<td>58 % (44% to 71%)</td>
<td>61 % (34% to 88%)</td>
<td>176</td>
<td>420 infected people in a population of 1000</td>
</tr>
</tbody>
</table>

### Circulating Cathodic Antigen test (CCA)

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value</th>
<th>Number of Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine POC Test</td>
<td>39 % (6% to 73%)</td>
<td>84 % (55% to 100%)</td>
<td>256</td>
<td>420 infected people in a population of 1000</td>
</tr>
</tbody>
</table>

### Comparisons

<table>
<thead>
<tr>
<th>Comparison Type</th>
<th>Comparison Type</th>
<th>Quantity of evidence and overall finding</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microhaematuria vs. Proteinuria</td>
<td>All studies</td>
<td>71 Microhaematuria vs. Proteinuria, Overall significant difference in accuracy (P =0.21)</td>
<td>There is no statistically significant difference in overall accuracy when microhaematuria and proteinuria are carried out and compared in different individuals</td>
</tr>
<tr>
<td>Paired studies (Tests done in the same individuals)</td>
<td>42 Microhaematuria vs. Proteinuria, Overall significant difference in accuracy (P =0.17)</td>
<td>There is no statistically significant difference in overall accuracy when microhaematuria and proteinuria are carried out and compared in the same individuals</td>
<td></td>
</tr>
</tbody>
</table>

---

**Summary of findings table for tests to detect S. mansoni**
What is the diagnostic accuracy of circulating antigen tests for *S. mansoni* infection?

<table>
<thead>
<tr>
<th>Patients/Population</th>
<th>People residing in areas endemic for <em>S. mansoni</em> infection (15 out of 86 studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior treatment with Praziquantel before baseline study</td>
<td>No (5 studies), Unclear (10 studies)</td>
</tr>
<tr>
<td>Prior testing</td>
<td>None</td>
</tr>
<tr>
<td>Settings</td>
<td>Field settings (Villages, schools &amp; military camp) in Africa and South America</td>
</tr>
<tr>
<td>Index tests</td>
<td>Circulating cathodic antigen test (CCA)</td>
</tr>
<tr>
<td>Reference standard</td>
<td>Stool microscopy</td>
</tr>
<tr>
<td>Importance</td>
<td>These tests are being used as replacements to conventional microscopy in disease control programs for schistosomiasis as they are rapid, easier to use and interpret, and may have comparable sensitivity to microscopy. As control programmes gain impetus and infection intensities decrease, higher sensitivities become a prerequisite for future diagnostics.</td>
</tr>
<tr>
<td>Studies</td>
<td>Cross sectional studies</td>
</tr>
<tr>
<td>Quality concerns</td>
<td>Poor reporting of patient characteristics, index test and reference standard methods, intensity of infection were common concerns. The risk of bias assessment for most included studies was largely unclear for the QUADAS domains; Patient Selection, Index and Reference tests</td>
</tr>
</tbody>
</table>

### Test types

<table>
<thead>
<tr>
<th>Test types</th>
<th>No. of evaluations</th>
<th>Average pooled results</th>
<th>Consequences in a cohort of 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>True prevalence of <em>S. mansoni</em></td>
</tr>
</tbody>
</table>

| Circulating Cathodic Antigen test (CCA) | 12 | Sens=87% (85% to 90%) | Spec=61% (51% to 70%) | 440 infected people in a population of 1000 | 57 | 218 | 60% |

| Urine POC Test | 12 | Sens=87% (85% to 90%) | Spec=61% (51% to 70%) | 440 infected people in a population of 1000 | 57 | 218 | 60% |
References


Circulating antigen tests and urine reagent strips for human schistosomiasis


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Chapter 8


Circulating antigen tests and urine reagent strips for human schistosomiasis


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