OPEN ACCESS

Systematic reviews of point-of-care tests for the diagnosis of urogenital *Chlamydia trachomatis* infections

Helen Kelly,[1] Cordelia E M Coltart,[1] Nitika Pant Pai,[2] Jeffrey D Klausner,[3] Magnus Unemo,[4] Igor Toskin,[5] Rosanna W Peeling[1]

[1]Department of Clinical Research, London School of Hygiene & Tropical Medicine, London, UK
[2]Department of Medicine, Division of Clinical Epidemiology, McGill University, Montreal, Quebec, Canada
[3]Department of Global Health, University of California, Los Angeles, California, USA
[4]WHO Collaborating Centre for Gonorrhoea and other STIs, Örebro University Hospital, Orebro, Sweden
[5]Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland

Correspondence to
Dr Rosanna W Peeling, Department of Clinical Research, International Diagnostics Centre, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK; rosanna.peeling@lshtm.ac.uk

Received 11 March 2017
Revised 29 May 2017
Accepted 3 June 2017

ABSTRACT

Background WHO estimates that 131 million new cases of urogenital *Chlamydia trachomatis* (CT) infections occur globally every year. Most infections are asymptomatic. Untreated infection in women can lead to severe complications. Screening and treatment of at-risk populations is a priority for prevention and control.

Objectives To summarise systematic reviews of the performance characteristics of commercially available point-of-care tests (POCT) for screening and diagnosis of urogenital CT infection.

Methods Two separate systematic reviews covering the periods 2004–2013 and 2010–2015 were conducted on rapid CT POCTs. Studies were included if tests were evaluated against a valid reference standard.

Results In the first review, 635 articles were identified, of which 11 were included. Nine studies evaluated the performance of eight antigen detection rapid POCTs on 10 280 patients and two studies evaluated a near-patient nucleic acid amplification test (NAAT) on 3518 patients. Pooled sensitivity of antigen detection tests was 53%, 37% and 63% for cervical swabs, vaginal swabs and male urine, and specificity was 99%, 97% and 98%, respectively. The pooled sensitivity and specificity of the near-patient NAAT for all specimen types were >98% and 99.4%, respectively. The second review identified two additional studies on four antigen detection POCTs with sensitivities and specificities of 22.7%–37.7% and 99.4%–100%, respectively. A new two-step 15 min rapid POCT using fluorescent nanoparticles showed performance comparable to that of near-patient NAATs.

Conclusions The systematic reviews showed that antigen detection POCTs for CT, although easy to use, lacked sufficient sensitivity to be recommended as a screening test. A near-patient NAAT shows acceptable performance as a screening or diagnostic test but requires electricity, takes 90 min and is costly. More affordable POCTs are in development.

INTRODUCTION

According to WHO estimates in 2012, urogenital chlamydial infection (etiological agent: *Chlamydia trachomatis*, CT) is the most common bacterial STI and approximately 131 million new cases occur globally every year.[1] The highest number of estimated cases was in the WHO Western Pacific Region (61 million), followed by the WHO American Region (25 million), WHO South-East Asian Region (14 million), WHO African Region (12 million), WHO Eastern Mediterranean Region (10 million) and WHO European Region (9 million).[1] Most CT infections are asymptomatic. Undetected, CT infection may result in severe complications such as pelvic inflammatory disease, ectopic pregnancy, infertility, and enhanced transmission and acquisition of HIV. Screening and treatment of at-risk populations is therefore a priority for prevention and control.

Highly accurate nucleic acid amplification tests (NAATs) are available in the developed world but since they require robust laboratory infrastructure and trained personnel, these NAATs are neither affordable nor accessible to patients in the developing world, where access to laboratories is limited and the STI burden remains high despite syndromic management. In the absence of screening programmes for asymptomatic infections and improved access to accurate laboratory diagnosis, the number of detected and reported cases is substantially lower than the number of real cases.[1]

NAATs are costly, technically demanding and laboratory based, requiring patients to come to the clinic to be screened and return for the result, or to mail in self-collected samples (vaginal swabs for women and urine specimens for men) and waiting for results to be sent by phone or internet.[2] Point-of-care tests (POCTs) that are affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free and delivered to end-users (ASSURED) would have considerable implications for STI control in less resourced settings and in well-resourced settings. Using accurate and rapid CT POCTs, patients can be promptly diagnosed and appropriately treated at presentation, preventing complications, and ongoing transmission, and offering opportunities for counselling and contact notification. Simple rapid POCTs for the diagnosis and screening of CT infections are commercially available, but there are limited data on their performance.[4 5] The WHO STI point-of-care (POC) diagnostic initiative, coordinated by the Department of Reproductive Health and Research at WHO, including the UNDP/UNFPA/Unicef/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, aims to facilitate and support access to quality-assured STI POCTs within national STI programmes through providing advice to WHO Member States and other relevant public health institutions on the performance and operational characteristics of new

To cite: Kelly H, Coltart CEM, Pant Pai N, *et al*. *Sex Transm Infect* 2017;**93**:S22–S30.

commercially available STI diagnostic tests that can be used at the POC across all countries.

This paper describes the findings from two systematic reviews of the performance and operational characteristics of commercially available POCTs for the diagnosis of urogenital and extragenital CT infection.

METHODS

The first systematic review

The first systematic review was conducted in 2013–2014 by authors from the London School of Hygiene and Tropical Medicine, UK, in collaboration with McGill University, Canada, in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, which aim to advance the reporting of systematic reviews and meta-analyses by improving the transparency and completeness of information.[6] Only rapid and simple POCTs that met the ASSURED criteria[3] were included.

Search terms and strategy

MEDLINE and GLOBAL HEALTH databases were searched from 1 January 2004 to 31 December 2013. Search terms were as follows: (chlamydia AND *Chlamydia trachomatis* AND *C. trachomatis*) AND (point-of-care OR POC test OR POCT OR rapid test* OR rapid assay* OR diagnos* OR near patient OR screening OR urine dipstick) AND (evaluation OR performance characteristics OR validation OR performance OR sensitivity OR specificity).

Systematic reviews were identified first. If no systematic reviews were published on the topic, case–control, cross-sectional or cohort studies were identified.

Inclusion criteria

Eligibility criteria were defined using PICOS (Population, Interventions, Comparisons, Outcomes, Study Design) criteria as shown in table 1. Studies evaluating the accuracy and/or precision of any CT POCT commercially available at the time of the review were considered for inclusion.

Exclusion criteria

Studies were excluded if the test was not a rapid test for CT, if diagnostic accuracies were not compared with an appropriate reference standard, and if the studies did not report data to allow for calculation of diagnostic accuracy. Studies reporting POCT analytical performance and POCTs in development were excluded.

Data extraction

Two reviewers independently extracted data from the included studies meeting the inclusion criteria. Items for data extraction for each POCT included: study (journal, author, year); location (country, healthcare level where study was performed); field/laboratory location where tested (peripheral/reference); test method; reference/gold standard; specimen type; sample size; population; age range; genital symptoms; sensitivity; specificity; positive predictive value; negative predictive value; receiver operating characteristics: number of steps; major equipment required for test; time to result; and CT prevalence. Disagreements were resolved by consensus or external advisors.

Data synthesis and statistical analysis

Descriptive analyses were performed using STATA V.14 (STATA, College Station, TX, USA). For each study, the sensitivity and specificity along with 95% CIs, compared with the reference standard, were calculated. Forest plots were generated to display sensitivity and specificity estimates.

Meta-analysis

The heterogeneity in the forest plots was assessed by visually examining the CIs of individual studies, and in summary Hierarchical Summary Receiver Operating Characteristic (HSROC) plots (by examining the width of the prediction region, with a wider prediction region suggesting more heterogeneity). Heterogeneity in terms of the sample types by index test for CT and also prespecified subgroups such as different specimen types were examined. A bivariate random-effects model was used and meta-analyses were carried out in STATA. For this review of CT POCTs, a meta-analysis for a predefined sample type was only carried out if at least four studies were available.

Metaregression

Additional heterogeneity was anticipated with respect to samples, patient population groups and prevalence within the prespecified subgroups. Therefore, a bivariate metaregression model in STATA was selected for use under the assumption that the pooled sensitivity and specificity were different in each subgroup, but not the between-study variance-covariance matrix. The metaregression assessment was performed only on studies with the same reference standard. It was also presumed that the effect of the covariate would not differ between the different reference standards.

Sensitivity analysis

Sensitivity analyses could not be performed due to lack of additional covariate data.

Table 1 Inclusion criteria (PICOS criteria)

Population	Any sexually active populations in any geographical location
Interventions (index tests)	Any commercially available technology used for *Chlamydia trachomatis* POCTs in the field (excluding those tested in laboratory settings)
Comparators	Studies using an acceptable reference standard that satisfy the STARD checklist (quality assessment) Acceptable reference standard—culture and/or NAAT
Outcomes	Evaluations of accuracy and/or precision. Include studies calculating sensitivity, specificity, PPV and NPV including 95% CI, ease of use and acceptability by user
Study design	Evaluation of studies published in peer-reviewed literature. No grey literature was included
Other	English language only, human subjects only, 1 January 2004 to 31 December 2013 Sample type: vaginal, cervical, urethral or urine samples

NAAT, nucleic acid amplification test; NPV, negative predictive value; PICOS, Population, Interventions, Comparisons, Outcomes, Study Design; POCT, point-of-care test; PPV, positive predictive value; STARD, Standards for the Reporting of Diagnostic Accuracy Studies.

Formal assessment of publication bias using methods such as funnel plots or regression tests was not performed because such techniques are not considered to be valid for diagnostic accuracy reviews.

Data quality

Quality of the studies included was assessed according to the STARD Criteria and Checklist.[7]

The second systematic review

The second systematic review was conducted in 2015 by authors from the University of California, Los Angeles, USA, for papers published from January 2010 to August 2015.[4]

Search terms and strategy

The search was conducted according to PRISMA guidelines[6] in PubMed using search terms as follows: sexually transmitted diseases or sexually transmitted infection* and chlamydia* and (point-of-care and (rapid test or diagnostic or screening or test)).

Abstracts of all search results and the full text of all potentially eligible articles were reviewed. This search yielded 61 articles whose abstracts were evaluated to determine whether they fit the inclusion criteria.

Inclusion criteria

The inclusion criteria were (1) publications including *Chlamydia* as STIs; (2) publications that date from January 2010 through August 2015; (3) publications relating to diagnostics; (4) publications published in English; and (5) original research.

Exclusion criteria

The exclusion criteria were (1) publications not covering CT; (2) publications including those infections but not in the sexually transmissible form; (3) publications published before 2010; and (4) publications not evaluating POC diagnostics using a valid reference standard assay.

Articles were sorted into the following subject categories and stratified based on: (1) performance evaluations, (2) cost analyses, (3) acceptability and feasibility trials and (4) proof of concept studies.

RESULTS

The first systematic review identified a total of 635 papers, of which 557 were excluded based on their title and abstract. An additional 68 articles were excluded after a review of the full text, leaving 10 articles for data extraction. An additional article was identified by a study adviser (figure 1).

The second review by Herbst de Cortina *et al* identified 33 articles, of which 8 were on the performance of tests to detect genital CT infection.[4] Of the eight studies, two evaluated the performance of Gram-stained urethral smears and one evaluated an automated urine flow cytometry compared with NAATs. Since microscopy and flow cytometry are not POCTs, they are not included in this review. Of the five studies included in this review, three were already identified in the first review and two studies published in 2015 and 2016 were added to the data extraction for this review.

Operational characteristics of POCTs included in the review

The two systematic reviews described the evaluation of nine brands of antigen detection POCTs and one NAAT that can be labelled as near patient as it is an automated sample-in answer-out assay that requires 2 min of hands-on time and is designed for both laboratories and clinic settings (table 2). The antigen detection tests included six immunochromatographic tests in a lateral format, one test using optical detection, one using enzyme detection and one using fluorescent nanoparticles.

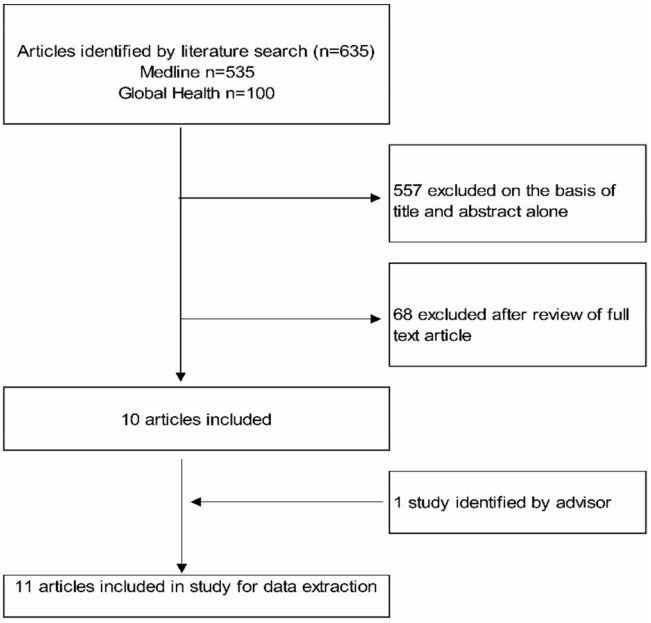

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for study selection in systematic review 1.

Data extracted from the studies

The two systematic reviews identified 11 studies that evaluated the performance of 9 brands of CT antigen detection POCTs on 11 889 study participants from 10 countries. Two studies described evaluation of the performance of a near-POC NAAT on 3568 study participants from two countries. Reference standard assays used included PCR assays (Roche Molecular Systems, USA), ligase chain reaction assay (Abbott Diagnostics, USA), strand displacement amplification assay, ProbeTec ET assay (Becton Dickinson, USA) and transcription-mediated amplification assay (Aptima, GenProbe, now Hologic, USA).

Table 3 displays data extracted from the studies evaluating the performance of CT antigen detection POCTs and near-POC NAAT in both systematic reviews.

Antigen detection rapid POCTs exhibited high specificity across all specimen types (range 97%–100%), the pooled sensitivity was 37% for vaginal swabs (95% CI 22.9% to 52.9%; range 17.1%–74.2%), 53% for endocervical swabs (95% CI 34.7% to 70.8%; range 22.7%–87%) and 63% for urine (95% CI 43.2% to 78.5%; range 49.7%–88.2%) (table 4). The aQcare Chlamydia TRF kit, which is a fluorescent nanoparticle-based lateral flow assay, was the best performing antigen detection POCT, with sensitivities and specificities comparable to that of near-patient NAATs.[8]

Although CT antigen detection rapid POCTs exhibited high specificity across all specimen types (range 97%–100%), the pooled sensitivity was 37% for vaginal swabs (95% CI 22.9% to 52.9%; range 17.1%–74.2%), 53% for endocervical swabs (95% CI 34.7% to 70.8%; range 22.7%–87%) and 63% for urine (95% CI 43.2% to 78.5%; range 49.7%–88.2%) (table 4). The aQcare Chlamydia TRF kit, which is a fluorescent nanoparticle-based lateral flow assay, was the best performing antigen

Table 2 *Chlamydia trachomatis* POCTs identified in the two systematic reviews

Test	Manufacturer	Type of test	Time to result	Room temperature storage	Studies
Point-of-care antigen detection tests					
ACON Chlamydia and NG/CT Duo	ACON, China	ICT	<30 min	Yes	Hurly *et al*[10] Nuñez-Forero *et al*[20]
aQcare Chlamydia TRF kit*	Medisensor, Korea	Lateral flow assay using fluorescent nanoparticles	15 min	Yes	Ham *et al*[21]
BioRapid	BioKit, Spain	ICT	20 min	Yes	van Dommelen *et al*[22]
BioStar Chlamydia†	Inverness Medical, USA	Optical immunoassay	30 min	Yes	Bandea *et al*[23]
Chlamydia Rapid Test	DRW, UK	ICT	25 min	Yes	Saison *et al*[24] Wisniewski *et al*[11] Nadala *et al*[25] van der Helm *et al*[26] Hurly *et al*[10]
Clearview	Alere, USA	ICT	30 min	Reagents storage at 2°C–8°C	Yin *et al*[8] Saison *et al*[24]
Chlamydia Test Card	Ultimed, Germany	ICT	10 min	Yes	Sabidó *et al*[27]
HandiLab-C	HandiLab, USA	Enzyme detection	<15 min	Yes	Michel *et al*[28] van Dommelen *et al*[22]
QuickVue	Quidel, USA	ICT	15 min	Yes	van Dommelen *et al*[22]
Near point-of-care NAAT					
Xpert CT/NG	Cepheid, USA	Real-time PCR	87 min	Yes	Goldenberg *et al*[13] Gaydos *et al*[12]

*aQcare Chlamydia TRF test is a quantitative assay which uses europium-chelated nanoparticles in a lateral flow format. The signal is measured using a portable, small fluorescence reader (dimensions 348×240×221 mm).
†The BioStar assay is an optical immunoassay which is a proprietary technology that allows direct visual detection of the binding reactions between antigens and antibodies on a thin film.
DRW, Diagnostics for the Real World; ICT, immunochromatographic test; NAAT, nucleic acid amplification test; POCT, point-of-care test.

detection POCT, with sensitivities and specificities comparable to that of near-patient NAATs.[8] The best performing test overall was the Xpert CT/NG, a Food and Drug Administration-approved real-time PCR assay.

The sensitivity of the Cepheid GeneXpert assay showed no significant difference between self-collected vaginal swabs (98.7%), cervical swabs (97.4%), female urine (97.6%) and male urine specimens (97.5%) with specificities ranging from 99.4% to 99.9%. The sensitivity and specificity of this assay for rectal swabs are 86.0% and 99.2% respectively. In particular, for POCTs we are interested in specimens that are easy to collect. The overall sensitivity and specificity of antigen detection POCTs for vaginal swabs from the two systematic reviews are graphically represented in figure 2A,B and those for urine specimens in figure 3A,B.

According to the STARD criteria[7] relevant to POCTs, the quality of the papers included was acceptable, with noted omissions in the categories describing whether operators were trained to perform the tests, mechanism for blinding between the results of the index and reference tests and documentation of the frequency of indeterminate results (table 5).

DISCUSSION

The two systematic reviews described in this paper showed that while the specificity of most CT antigen detection POCTs was >97%, their sensitivities were suboptimal, especially when used with vaginal swabs. Nevertheless, they are being used, especially in countries lacking the capacity for stringent regulatory review and approval. Women who had false negative test results due to low sensitivity would not be treated and could subsequently develop long-term reproductive sequelae such as pelvic inflammatory disease, ectopic pregnancy and tubal infertility. Using a model, Gift *et al*[9] showed that a POCT with a sensitivity of 65% can lead to more patients being treated for genital chlamydial infections than a more accurate NAAT because only 50% of patients who were screened for chlamydia returned for their test results within 3 weeks. Moreover, by the time they returned, 3% of women had developed pelvic inflammatory disease. Hence, POCTs offer an important opportunity to treat any infected patient and initiate partner notification in the same clinic visit.

Although the sensitivity of POCTs is higher for cervical swabs than vaginal swabs, POCTs are best used with specimens that are easy to collect such as urine for men or vaginal swabs, which are self-collected or collected by a healthcare provider. Hurly *et al*[10] compared the performance of the Chlamydia Rapid Test (Diagnostics for the Real World, Cambridge, UK) and ACON CT test for men and women, and found lower sensitivities for urine from men (41.4%–43.8%) compared that for vaginal swabs (66.7%–74.2%) for both POCTs. The authors attributed this difference to the CT load in these specimen types. Wisniewski *et al*[11] showed that for urine samples, there is significantly more chlamydia in the first 4–5 mL of the void than subsequent aliquots.

A single study on a POCT based on fluorescent nanoparticles requiring only 15 min turnaround time showed promising performance characteristics that are comparable to near-patient NAATs. More evaluations of this POCT would be necessary to determine if these performance characteristics are reproducible.

Gaydos *et al*[12] evaluated both symptomatic and asymptomatic women at reproductive health clinics, and showed excellent accuracy for the Cepheid Xpert CT/NG test. In contrast to the antigen detection POCTs, the Xpert CT/NG did not show any significant difference in performance between specimen types. Goldenberg *et al*[13] showed that the Xpert test has adequate

Table 3 Data from studies evaluating the performance of *Chlamydia trachomatis* antigen detection POCT

Study/year/location	Test evaluated	Specimen	Reference assay	Sample size/population (% CT prevalence)	Sensitivity (95% CI)*	Specificity (95% CI)*	PPV	NPV
Bandea *et al* (2009)[23] USA	BioStar Optical Immunoassay	Cervical swab	Abbott ligase chain reaction	261 female adolescents (16%)	59.4%	98.4%	–	–
Hurly *et al* (2014)[10] Vanuatu	Acon Chlamydia Rapid Test	Vaginal swab	Roche Cobas TaqMan PCR assay	75 women Reproductive clinic	66.7% (22.3% to 95.7%)	91.3% (82.0% to 96.7%)	40%	96.9%
	Acon Chlamydia Rapid Test	Urine	Roche Cobas TaqMan PCR assay	133 men Reproductive clinic	43.8% (19.8% to 70.1%)	98.3% (93.9% to 99.8%)	77.8%	92.7%
	DRW Chlamydia Rapid Test	Vaginal swab	Roche Cobas TaqMan PCR assay	223 women Reproductive clinic	74.2% (61.5% to 84.5%)	95.7% (91.3% to 98.2%)	86.8%	90.6%
	DRW Chlamydia Rapid Test	Urine	Roche Cobas TaqMan PCR assay	156 men Reproductive clinic	41.4% (23.5% to 61.1%)	89.0% (82.2% to 93.8%)	46.2%	86.9%
Michel *et al* (2009)[28] Philippines	HandiLab-C	Vaginal swab	Abbott m2000 PCR assay	231 women (17%)	17.9%	90.6%	28%	85%
Nadala *et al* (2009)[25] UK	DRW Chlamydia Rapid Test	Urine	Roche Cobas TaqMan PCR assay	1211 men GUM clinic (9.1%)	82.6% (74.1% to 89.2%)	98.5% (97.5% to 99.1%)	84.1%	98.3%
Sabidó *et al* (2009)[27] Guatemala	Chlamydia Test Card	Endocervical swab	Roche Amplicor PCR assay	276 women STI clinic (9.8%)	63.0%	99.6%	94%	96%
Saison *et al* (2007)[24] Philippines	Clearview Chlamydia Test	Vaginal swabs	Roche Amplicor PCR assay	333 women STI clinic (18.3%)	31.1	95.2	59%	86%
		Cervical swabs		822 women STI clinic (19.3%)	53.5%	99.1%	93%	90%
	DRW Chlamydia Rapid Test	Vaginal swabs	Roche Amplicor PCR assay	1129 women STI clinic and OB/Gyn clinic (12.9%)	76.7%	99.6%	91.8%	96.6%
van der Helm *et al* (2012)[26] Suriname	DRW Chlamydia Rapid Test	Vaginal swab	Hologic Aptima assay	912 women STI/sexual health clinic (9.2%–20.8%)	41.2% (31.9% to 50.9%)	96.4% (95.0% to 97.5%)	59.2%	92.9%
van Dommelen *et al* (2010)[22] Netherlands	QuickVue Chlamydia Rapid Test	Vaginal swab, self-collected	Roche Cobas Amplicor PCR assay	737 women STI clinic (11%)	27.3%	99.7%	91.3%	92.2%
	HandiLab-C	Vaginal swab, self-collected	Roche Cobas Amplicor PCR assay	378 women STI clinic (11%)	11.6%	91.9%	15.6%	89.0%
	BioRapid Chlamydia Antigen Test	Vaginal swab, self-collected	Roche Cobas Amplicor PCR assay	737 women STI clinic (11%)	17.3%	93.5%	24.6%	90.4%
Wisniewski *et al* (2008)[11] UK	DRW Chlamydia Rapid Test	Urine—urine cup	Roche Amplicor PCR assay	534 men STI clinic (6.4%)	47% (30% to 64%)	98.8% (97.9% to 99.8%)	–	–
		Urine—FirstBurst sample			82% (70% to 95%)	98.8% (97.9% to 99.8%)	–	–
Yin *et al* (2006)[8] China	Clearview Chlamydia Rapid Test	Vaginal swab	Roche Amplicor PCR assay	1497 women STI clinic (13%)	32.8% (26.5% to 39.9%)	99.2% (98.4% to 99.6%)	85.7%	90.5%

Continued

Table 3 Continued

Study/year/location	Test evaluated	Specimen	Reference assay	Sample size/population (% CT prevalence)	Sensitivity (95% CI)*	Specificity (95% CI)*	PPV	NPV
		Cervical swabs			49.7% (42.6% to 56.9%)	97.9% (96.9% to 98.6%)	78.4%	92.8%
Additional studies identified in second systematic review (Herbst de Cortina *et al*[4])								
Ham *et al* (2015)[21] South Korea	aQcare Chlamydia kit	Cervical swab	AccuPower CT and NG/RT PCR assay	348 women (27.8%)	93.8% (88.6% to 97.0%)	96.8% (94.8% to 98.1%)	91.9%	97.6%
	aQcare Chlamydia kit	Urine	AccuPower CT and NG/RT PCR assay	93 men and women (18.3%)	88.2% (67.4% to 97.7%)	94.7% (90.1% to 96.9%)	78.9%	97.3%
Nuñez-Forero *et al* (2016)[20] Colombia	Acon Chlamydia Rapid Test	Cervical swab	Roche Cobas Amplicor PCR assay	229 women with lower UTI symptoms	22.7% (2.9% to 42.5%)	100% (99.7% to 100%)	–	–
	Acon Chlamydia/ Gonorrhoea Rapid Test	Cervical swab	Roche Cobas Amplicor PCR assay	491 women with lower UTI symptoms	30.5% (17.9% to 43.1%)	99.8% (99.2% to 100%)	–	–
	QuickVue Chlamydia Rapid Test	Cervical swab	Roche Cobas Amplicor PCR assay	664 women with lower UTI symptoms	37.7% (23.7% to 51.7%)	99.4% (98.6% to 100%)	–	–
Near-patient molecular assays								
Gaydos *et al* (2013)[12] USA	Cepheid GeneXpert CT/NG	Vaginal swab, self-collected	Hologic Aptima and BD ProbeTec assays	1772 women and 1387 men STI, OB/ Gyn, teen, family planning clinics	98.7% (93.1% to 100%)	99.4% (98.9 to 99.7)	88.6%	99.9%
		Cervical swab			97.4% (91.0% to 99.7%)	99.6% (99.1% to 99.8%)	91.6%	99.9%
		Urine—female			97.6% (91.5% to 99.7%)	99.8% (99.5% to 100%)	96.4%	99.9%
		Urine—male			97.5% (91.4% to 99.7%)	99.9% (99.6% to 100%)	98.7%	99.8%
Goldenberg *et al* (2012)[13] UK	Cepheid GeneXpert CT/NG	Rectal swab	Hologic Aptima assay	409 men (10.5%)	86.0% (72.1% to 94.7%)	99.2% (97.6% to 99.8%)	92.5%	98.4%

*95% CIs are shown when available.
NPV, negative predictive value; POCT, point-of-care test; PPV, positive predictive value; UTI, urinary tract infection.

Table 4 Pooled performance of the POC antigen detection and near-patient NAATs for different specimen types

	Antigen detection point-of-care tests			Near-patient NAATs		
Specimen type	Number of studies; N	Sensitivity (95% CI)	Specificity (95% CI)	Number of studies; N	Sensitivity % (95% CI)	Specificity % (95% CI)
Cervical swab	8; 4588	53.1% (34.7 to 70.8)	98.9% (98.0 to 99.4)	1; 1713	97.4%	99.6%
Vaginal swab	10; 6252	36.6% (22.9 to 52.9)	96.9% (94.0 to 98.4)	1; 1710	98.7%	99.4%
Male urine	5; 2568	62.5% (43.2 to 78.5)	98.0% (95.1 to 99.0)	1; 1386	97.5%	99.9%
Female urine	–	–	–	1; 1718	97.6%	99.8%
Male rectal swab	–	–	–	1; 409	86%	99.2%

NAAT, nucleic acid amplified test; POC, point of care.

performance with rectal swabs. Although more accurate, near-patient NAATs are more expensive than antigen detection POCTs. However, the Cepheid platform has two features which are advantages. First, it allows random access in that detection of different pathogens on its test menu can be initiated any time as each cell is an independent nucleic acid amplification and detection reaction. Second, the Cepheid platform, like most other near-patient molecular platforms, is polyvalent in that the equipment can be used with cartridges for over 20 pathogens. This makes the testing more cost-effective.

In selecting a test for screening of asymptomatic populations or diagnosis of symptomatic patients, health providers and control programmes need to consider the trade-off between accuracy and affordability for their epidemiological setting and what patients are willing to pay and whether they are willing to wait for 90 min versus 15–30 min. Gift *et al*

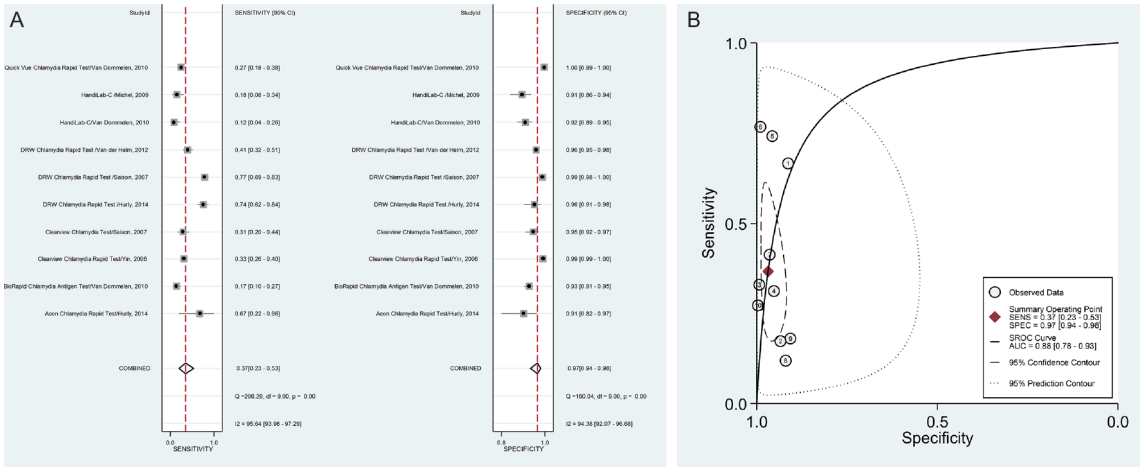

Figure 2 (A) Meta-analysis of *Chlamydia trachomatis* antigen detection POC test performance using vaginal swabs in 10 studies. (B)HSROC for *C. trachomatis* antigen detection POC test performance using vaginal swabs in 10 studies. AUC, area under the curve; POC, point of care; SENS, sensitivity; SPEC, specificity.

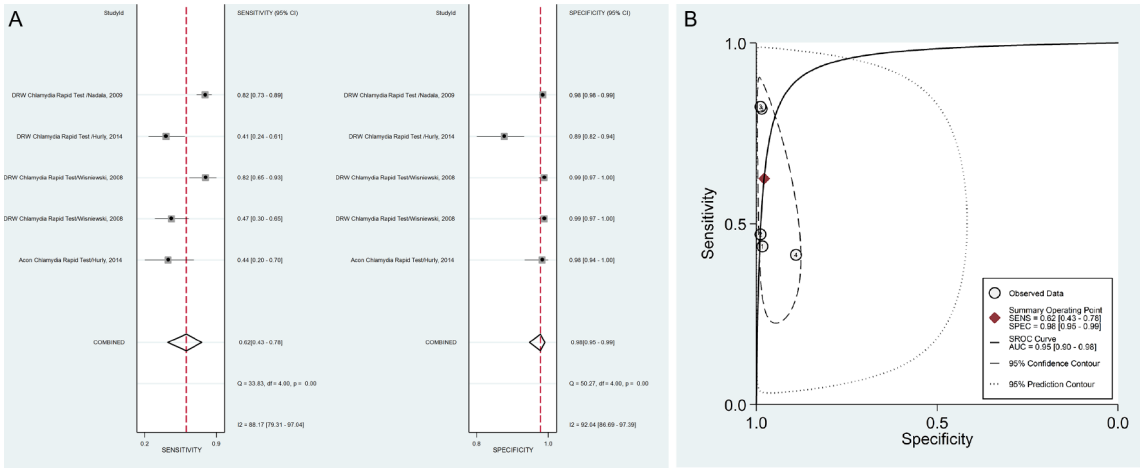

Figure 3 (A) Meta-analysis of *Chlamydia trachomatis* antigen detection POC test performance using urine samples in five studies among men. (B) HSROC for *C. trachomatis* antigen detection POC test using urine samples in 5five studies among men. AUC, area under the curve; POC, point of care; SENS, sensitivity; SPEC, specificity.

Table 5 Assessment of the quality of the studies included in the first systematic review

STARD criteria[7]	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
1. Easily identifiable as a study of diagnostic accuracy										
2. State the research questions or study aims										
3. Describes the study population: the inclusion and exclusion criteria, the setting and the locations where the data were collected										
4. Describes participant recruitment and sampling (prospective or retrospective study)										
5. Describes the test under evaluation										
6. Describes the reference standard and its rationale										
7. Describes specimen acquisition										
8. Describes specimen storage										
9. Describes training in specimen processing										
10. Describes blinding mechanism between index and reference test results										
11. Uses appropriate statistical analysis										
12. Shows cross-tabulation of results of index and reference tests										
13. Estimates diagnostic accuracy with statistical uncertainty (CIs)										
14. Shows how indeterminate results are handled										
15. Describes variability and subgroup analysis										
16. Discusses clinical applicability of findings										

described the rapid test paradox in a model of chlamydial screening in which a rapid test of 65% sensitivity led to more infected patients being treated than using a NAAT with higher accuracy because of low patient return rates for results.[9] Adams *et al*[14] examined the need to modify patient pathways to take full advantage of near-patient NAATs, which can reduce cost and clinician time and may lead to more efficient and appropriate care for patients compared with standard of care which is off-site laboratory testing and having to return for test results and treatment. In a simulation of 1.2 million patients seeking STI care across the UK, it was estimated that POC testing can be cost-saving and reduce overtreatment of patients who are diagnosed using a syndromic approach.[15] POC testing in this scenario can prevent 189 cases of pelvic inflammatory disease and 17 561 cases of onward transmission.

The quality of the studies included in these systematic reviews is generally satisfactory (table 5). The main shortcomings include omission in describing training in specimen storage and processing, how indeterminate results are managed, and blinding between index and reference test results.

Our review had several limitations. First, the first systematic review only used MEDLINE and GLOBAL HEALTH databases and the second systematic review only used PubMed to find relevant articles. Second, there are existing commercial POCTs which have been approved for use but were not evaluated in any publications between January 2000 and August 2015, preventing their inclusion in this paper. A number of studies that are proof of concept studies or analytical performance studies from promising new technology platforms have not been included. They were described in the second systematic review.[4]

Emerging new technologies, including isothermal amplification technologies, promise major advancements in the field of rapid POCTs for STIs in the near future.[16] A number of novel POC molecular platforms have been developed for HIV early infant diagnosis and viral load and are now being adapted for the diagnosis of STIs.[17 18] As more of these molecular POCTs become available, the cost to produce, distribute and use these tests will also decrease, thus increasing accessibility and affordability in less resourced settings, where STI prevalence is highest and the burden of adverse outcomes is greatest.[19]

CONCLUSIONS

The systematic reviews showed that antigen detection POCTs for CT, although easy to use, lacked sufficient sensitivity to be recommended as screening tests. Currently available near-POC NAATs have acceptable performance characteristics to be used as screening and diagnostic tests but need a source of electricity, have a relatively long turnaround time of approximately 90 min and are too costly for widespread use, especially in low resource settings. Other novel POC molecular assays are under development and may soon be available to improve chlamydial screening and diagnosis in less resourced settings as well as more well-resourced settings. However, before the introduction of these novel POCTs it is crucial to evaluate their performance and operational characteristics and their acceptability to patients and healthcare facilities. This is a high priority for the WHO STI POC diagnostic initiative in the coming years as countries strive to reduce the burden of STIs.

Acknowledgements We are grateful to Rachel Chater for assistance with the preparation of the manuscript.

Key messages

- Diagnostic tests are needed for detecting genital chlamydial infections but there are limited data on their performance and operational characteristics for use in the developing world. Systematic reviews show that antigen detection tests that can be used at the point of care (POC) have good specificity but suboptimal sensitivity.
- Near-patient molecular assays are highly accurate but require electricity, 90 min turnaround time and are too costly for use in low resource settings.
- Promising novel POC technologies that are accurate have shorter turnaround time and are less costly in development.

Contributors RWP and IT designed the review. HK and CEMC conducted the searches and data extraction. NPP performed the analyses. All authors contributed to the finalisation of the manuscript.

Funding This work was funded by the UNDP-UNFPA-Unicef-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), a cosponsored programme executed by WHO (Contract No SPHQ13-APW-4095).

Disclaimer The author(s) is(are) staff member(s) of the World Health Organization. The author(s) alone is(are) responsible for the views expressed inthis publication and they do not necessarily represent the views,decisions or policies of the World Health Organization.

Competing interests None declared.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES

1 Newman L, Rowley J, Vander Hoorn S, *et al*. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global Reporting. *PLoS One* 2015;10:e0143304.
2 Unemo M, Ballard R, Ison C, *et al*. *Laboratory diagnosis of sexually transmitted infections, including HIV*. Geneva, Switzerland: WHO, 2013.
3 Peeling RW, Holmes KK, Mabey D, *et al*. Rapid tests for sexually transmitted infections (STIs): the way forward. *Sex Transm Infect* 2006;82(suppl 5):v1–6.
4 Herbst de Cortina S, Bristow CC, Joseph Davey D, *et al*. A systematic review of point of care testing for chlamydia trachomatis, neisseria gonorrhoeae, and trichomonas vaginalis. *Infect Dis Obstet Gynecol* 2016;2016:ID 4386127.
5 Gaydos C, Hardick J. Point of care diagnostics for sexually transmitted infections: perspectives and advances. *Expert Rev Anti Infect Ther* 2014;12:657–72.
6 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
7 Cohen JF, Korevaar DA, Altman DG, *et al*. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ Open* 2016;6:e012799. http://bmjopen.bmj.com/content/6/11/e012799.abstract
8 Yin YP, Peeling RW, Chen XS, *et al*. Clinic-based evaluation of Clearview chlamydia MF for detection of *Chlamydia trachomatis* in vaginal and cervical specimens from women at high risk in China. *Sex Transm Infect* 2006;82(suppl V):v33–7.
9 Gift TL, Pate MS, Hook EW, *et al*. The rapid test paradox: when fewer cases detected lead to more cases treated: a decision analysis of tests for *Chlamydia trachomatis*. *Sex Transm Dis* 1999;26:232–40.
10 Hurly DS, Buhrer-Skinner M, Badman SG, *et al*. Field evaluation of the CRT and ACON Chlamydia point-of-care tests in a tropical, low-resource setting. *Sex Transm Infect* 2014;90:179–84.
11 Wisniewski CA, White JA, Michel CE, *et al*. Optimal method of collection of first-void urine for diagnosis of Chlamydia trachomatis infection in men. *J Clin Microbiol* 2008;46:1466–9.
12 Gaydos CA, Van Der Pol B, Jett-Goheen M, *et al*. Performance of the Cepheid CT/NG Xpert rapid PCR test for detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. *J Clin Microbiol* 2013;51:1666–72.
13 Goldenberg SD, Finn J, Sedudzi E, *et al*. Performance of the GeneXpert CT/NG assay compared to that of the Aptima AC2 assay for detection of rectal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* by use of residual aptima samples. *J Clin Microbiol* 2012;50:3867–9.
14 Adams EJ, Ehrlich A, Turner KM, *et al*. Mapping patient pathways and estimating resource use for point of care versus standard testing and treatment of Chlamydia and gonorrhoea in genitourinary medicine clinics in the UK. *BMJ Open* 2014;4:e005322.
15 Turner KM, Round J, Horner P, *et al*. An early evaluation of clinical and economic costs and benefits of implementing point of care NAAT tests for *Chlamydia trachomatis* and *Neisseria* gonorrhoea in genitourinary medicine clinics in England. *Sex Transm Infect* 2014;90:104–11.
16 WHO STI POC Diagnostics landscape. http://who.int/reproductivehealth/topics/rtis/Diagnostic_Landscape_2016.pdf?ua=1 (accessed Mar 2 2017).
17 HIV/AIDS diagnostics technology landscape – semi-annual update. *UNITAID* www.unitaid.eu/images/UNITAID_2013_Semi-annual_Update_HIV_Diagnostics_Technology_Landscape.pdf
18 Peeling RW, McNerney R. Emerging technologies in point-of-care molecular diagnostics for resource-limited settings. *Expert Rev Mol Diagn* 2014;14:525–34.
19 Adachi K, Nielsen-Saines K, Klausner JD. *Chlamydia trachomatis* infection in Pregnancy: the global challenge of preventing adverse pregnancy and infant outcomes in Sub-Saharan Africa and Asia. *Biomed Res Int* 2016;2016:1–21.
20 Nuñez-Forero L, Moyano-Ariza L, Gaitán-Duarte H, *et al*. Diagnostic accuracy of rapid tests for sexually transmitted infections in symptomatic women. *Sex Transm Infect* 2016;92:24–8.
21 Ham JY, Jung J, Hwang BG, *et al*. Highly sensitive and novel point-of-care system, aQcare Chlamydia TRF kit for detecting *Chlamydia trachomatis* by using europium (Eu) (III) chelated nanoparticles. *Ann Lab Med* 2015;35:50–6.
22 van Dommelen L, van Tiel FH, Ouburg S, *et al*. Alarmingly poor performance in *Chlamydia trachomatis* point-of-care testing. *Sex Transm Infect* 2010;86:355–9.
23 Bandea CI, Koumans EH, Sawyer MK, *et al*. Evaluation of the Rapid BioStar Optical immunoassay for detection of *Chlamydia trachomatis* in Adolescent women. *J Clin Microbiol* 2009;47:215–6.
24 Saison F, Mahilum-Tapay L, Michel CE, *et al*. Prevalence of *Chlamydia trachomatis* infection among low- and high-risk Filipino women and performance of *Chlamydia* rapid tests in resource-limited settings. *J Clin Microbiol* 2007;45:4011–7.
25 Nadala EC, Goh BT, Magbanua JP, *et al*. Performance evaluation of a new rapid urine test for chlamydia in men: prospective cohort study. *BMJ* 2009;339:b2655.
26 van der Helm JJ, Sabajo LO, Grunberg AW, *et al*. Point-of-care test for detection of urogenital chlamydia in women shows low sensitivity. A performance evaluation study in two clinics in Suriname. *PLoS One* 2012;7:e32122.
27 Sabidó M, Hernández G, González V, *et al*. Clinic-based evaluation of a rapid point-of-care test for detection of *Chlamydia trachomatis* in specimens from sex workers in Escuintla, Guatemala. *J Clin Microbiol* 2009;47:475–6.
28 Michel CE, Saison FG, Joshi H, *et al*. Pitfalls of internet-accessible diagnostic tests: inadequate performance of a CE-marked Chlamydia test for home use. *Sex Transm Infect* 2009;85:187–9.