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Performance and operational characteristics of point-of-care tests for the diagnosis of urogenital gonococcal infections

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ABSTRACT

Background In 2012, there was an estimated 78 million new cases of gonorrhoea globally. Untreated infection may lead to reproductive and neonatal morbidity and facilitate HIV transmission. Diagnosis and treatment are a priority for control and prevention, yet use of point-of-care tests (POCTs) for *Neisseria gonorrhoeae* (NG) is limited.

Objectives To review the performance and operational characteristics of NG POCTs for diagnosis of urogenital gonorrhoea.

Methods We compiled and synthesised findings from two separate systematic reviews which included evaluations published until August 2015.

Results Six tests were included: five were immunochromatographic tests (ICTs) or optical immunoassay (OIAs) based on antigen detection; with 5–7 steps and results in 25–40 min, and one (GeneXpert CT/NG) was a 'near-patient test' based on nucleic acid amplification technique (NAAT); with three steps, electricity required, and results in 90 min. When compared with laboratory-based NAATs as the reference tests, sensitivities of ICT and OIA-based POCTs ranged from 12.5% to 70% when cervical/vaginal swabs were tested. Specificities ranged from 89% to 99.8%. The near-patient NAAT had sensitivities of >95% and specificities of >99.8% consistently across all specimen types (urine, cervical and vaginal swabs).

Conclusions Based on a limited number of evaluations, antigen detection POCTs for NG lacked sufficient sensitivity to be used for screening. A near-patient NAAT has acceptable performance, only involved a few steps, but needs electricity, a temperature-controlled environment and has a 90 min run time. To achieve wider scale up of NG POCTs, we need strong evidence of cost-effectiveness, which should inform guidelines and ultimately increase test development, demand and reduce costs.

INTRODUCTION

Gonococcal infection (or gonorrhoea), caused by the bacterium *Neisseria gonorrhoeae* (NG), is a curable STI. In 2012, WHO estimated that 78 million new cases of gonorrhoea occurred globally.¹ Uncomplicated gonorrhoea is characterised by abnormal vaginal discharge, bleeding and dysuria in women, and may result in urethral discharge and dysuria in men.^{2,3} Infections of the rectum and pharynx, which are mostly asymptomatic, can occur in both sexes.⁴ The majority of urogenital infections in women are

asymptomatic; and in men approximately half of infections can be asymptomatic.^{2,5} Untreated infection can lead to serious reproductive complications such as pelvic inflammatory disease, infertility and ectopic pregnancy in women and epididymo-orchitis in men.⁴ Untreated infection in pregnancy may lead to preterm birth.⁶ Babies born to infected mothers may develop ophthalmia neonatorum, resulting in blindness.⁷ Gonorrhoea has been associated with an increased risk of acquiring and transmitting HIV,⁸ including perinatal transmission.⁹ The mainstay for control of gonorrhoea is effective diagnostics and subsequent antimicrobial treatment; however, due to widespread antimicrobial resistance, therapeutic options have become very limited in recent years.¹⁰ Accordingly, dual antimicrobial therapy (mostly ceftriaxone plus azithromycin) has been introduced in well-resourced settings.¹¹ Diagnostic tests of high performance are key for early detection to guide treatment to prevent the development of sequelae and adverse pregnancy outcomes and interrupt onward transmission.

Traditionally, culture of NG was the gold standard for diagnosis. However, with the development of highly sensitive and specific nucleic acid amplification technologies (NAATs) in the past decade, which are both more forgiving in terms of specimen collection and transport than culture techniques and are highly automated, these assays are now the diagnostic of choice across laboratories in more-resourced settings.¹² In low-and-middle-income countries (LMICs), such laboratory services are either not available, or where limited services are available, patients many not be able to pay for or physically access these services. In these settings, syndromic management is widely implemented. Unfortunately, this approach does not work well for some syndromes, particularly the syndrome of vaginal discharge and fails to identify those with asymptomatic infection, leaving a large untreated population pool at risk of complications and ongoing transmission.¹³ Syndromic-guided management thus represents a clinical approach that can enhance presumptive, inappropriate antibiotic treatment of symptomatic subjects, potentially increasing the risk of antimicrobial resistance development, which represents an urgent challenge for NG in this age of 'antibiotic stewardship'.¹⁰

Globally, the development and application of point-of-care tests (POCTs) for curable STIs is recognised as an important approach to overcome



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the barriers to access and timeliness of diagnosis, a key priority in the control of curable STIs. According to the ASSURED criteria, POCTs should be affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free and deliverable.¹⁴ However, others have broadened this framework to include any diagnostic tool that can provide accurate results and facilitate treatment within the same clinical visit as testing, a definition that includes some NAATs that do not fit the classic ASSURED criteria.¹⁵ Simple rapid POCTs for the diagnosis of gonorrhoea are commercially available; however, these POCTs have traditionally suffered from low sensitivity. Emerging new technologies, including amplification technologies, promise major advances in the field of rapid POCTs for NG in the near future. The WHO STI POC Diagnostic Initiative has been 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 (<http://www.who.int/reproductivehealth/topics/rtis/pocts/en/>). The need to accelerate development and thereby access to NG POCTs and testing, particularly in LMIC, have been emphasised in the Global Health Sector Strategy on STIs that was endorsed at the 69th World Health Assembly in May 2016.¹⁶

Two recent comprehensive systematic reviews of POCTs for urogenital gonorrhoea have been published covering consecutive time periods up to August 2015: the first by Watchirs-Smith *et al* in 2001¹⁷ and the second by Herbst de Cortina *et al* in 2016.¹⁸ This paper synthesises the findings reported in these reviews as they relate to the performance and operational characteristics of commercially available POCTs for the diagnosis of urogenital NG infection.

METHODS

Both systematic reviews were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.¹⁹

Systematic review 1

The first review by Watchirs-Smith *et al*¹⁷ searched both PubMed and Embase using a comprehensive search term including 'rapid test', or 'POC test', or 'POCT' or 'LE' or 'urine dipstick', AND 'gonococcal', or 'gonorrhoea', or 'N gonorrhoeae' AND 'evaluation' or 'performance characteristics' or 'validation' or 'performance' or 'sensitivity' or 'specificity'. The search was limited to English-language publications and to the period prior to August 2010. The authors defined rapid POC testing as any system that provided rapid gonorrhoea diagnosis results at the point of care and could be conducted with minimal operator skill and infrastructure. The identified papers were reviewed and information was extracted by two authors independently. Disagreements were resolved by discussion and consensus. Papers were included if the reference standard for comparison was laboratory-based NAAT or bacterial culture. Papers were excluded if the test was conducted on clinical isolates rather than field samples or if the paper did not report primary data or only described the application and did not report on performance of the test.

Systematic review 2

The second review by Herbst de Cortina *et al*¹⁸ also used a comprehensive search term of a compilation of medical subject headings, text words and subheadings to search PubMed (sexually transmitted diseases or sexually transmitted infection* and (chlamydia or gonorrh* or trichom*)) and (point-of-care and

(rapid test or diagnostic or screening or test)). The search was limited to English-language publications and included the period of January 2010 to August 2015. The authors had a broader scope for their review and were interested in a search that included publications relating to diagnostic performance, cost analyses, acceptability and proof-of-concept studies and also, in addition to NG, they included *Chlamydia trachomatis* (CT) and *Trichomonas vaginalis* (TV). Exclusion criteria included those papers reporting on these infections but not in the sexually transmissible form as stated by the review authors.

For all papers meeting the inclusion criteria, information was extracted on the setting, participants (age, sex, genital symptoms), evaluation design (sample size, specimen type), POCT (type, manufacturer, brand name), gold standard reference test (NAAT, culture or microscopy), POCT performance (sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)) and for the first review, operational characteristics (number of steps, major equipment, time to result).

Although microscopy can be used to complement syndromic management at the point of care, in particular to exclude gonococcal urethritis in men, this method was not included in our present review as its focus is near-patient antigen or DNA detection techniques.

RESULTS

The literature search conducted by Watchirs-Smith *et al*¹⁷ identified 100 papers in total, including 14 in their published review paper: 9 were on leucocyte esterase (LE) dipsticks, 2 were on microscopy and 3 were on POCT for NG. The systematic review literature search by Herbst de Cortina *et al*¹⁸ identified 61 papers in total, 33 of which were included in the qualitative synthesis reported in their paper: 4 of these related to detection of NG (3 were POCT and 1 was traditional Gram stain microscopy) (table 1). For this overview, the papers related to evaluations of LE dipsticks and microscopy were excluded as they did not detect NG specifically (n=12).

Based on these two recent comprehensive systematic reviews,^{17 18} a total of six studies were identified from the published literature prior to August 2015 reporting on the performance of six diagnostic tests designed to detect NG and suitable for use at the POC. Table 2 summarises the extracted data from these studies. The POCTs evaluated included the GC Check (PATH, Seattle, Washington, USA),²⁰ BioStar (GC OIA) (ThermoFisher/BioStar, Boulder, Colorado, USA),^{21 22} Binax NOW Gonorrhoea Test (Inverness),²³ GeneXpert CT/NG (Cepheid, Sunnyvale, California, USA),²⁴ ACON Duo²⁵ and NG ACON Plate (ACON NG) (ACON Laboratories, San Diego, California, USA).²⁵ The ACON Duo, NG ACON, GC Check and Binax NOW are lateral flow immunochromatographic tests (ICTs); the BioStar is an optical immunoassay (OIA) tests; the GeneXpert CT/NG assay is based on NAAT (this test is referred to as a 'near-patient NAAT' hereafter because of the longer time to results than traditional POCTs). Two tests (GeneXpert and Acon Duo) are designed to detect presence of both NG and CT simultaneously from the same patient sample; however, only the results for the NG component are included here. The GeneXpert is also the only test designed to detect two highly conserved, non-chromosomal NG targets that are unique to NG and not found in other *Neisseria* species.

Most tests were each only evaluated in one study, although one OIA (Biostar OIA) was evaluated in two studies.^{21 22} Evaluations were conducted in 5958 patients across a range of settings (public and sexual health clinics, family planning and obstetrics/

Table 1 Comparison of two published systematic reviews regarding point-of-care tests (POCTs) for detection of *Neisseria gonorrhoeae*

	Review #1 (Watchirs-Smith <i>et al</i>) ¹⁷	Review #2 (Herbst de Cortina <i>et al</i>) ¹⁸
Focus	POCTs for NG (operational characteristics and performance)	POCT diagnostics for NG, CT, TV (performance, cost analyses acceptability and feasibility trials, proof of concept)
Language	English only	English only
Time	Prior to August 2010	January 2010 to August 2015
Search	PubMed, Embase	PubMed
Search terms	'rapid test', or 'POC test', or 'POCT' or 'LE' or 'urine dipstick', AND 'Gonococcal', or 'gonorrhoea', or 'N gonorrhoeae' AND 'evaluation' or 'performance characteristics' or 'validation' or 'performance' or 'sensitivity' or 'specificity'	Sexually transmitted diseases or sexually transmitted infection* and (chlamydia or gonorrh* or trichom*) and (point-of-care and (rapid test or diagnostic or screening or test))
Papers: yield/included	100/14	61/33
Papers with NG focus	14	4

CT, *Chlamydia trachomatis*; NG, *Neisseria gonorrhoeae*; TV, *Trichomonas vaginalis*.

gynaecology (OBGYN) clinics and a urology department) and in six countries (the USA, the UK, Benin, Brazil, Columbia and Japan). The percentage of symptomatic clients in the study population ranged from 5.4% to 100%; however, most study populations were largely drawn from symptomatic clients.

Most tests were compared with laboratory-based NAATs as the reference standard, while two were compared with culture alone; one was compared with laboratory-based NAAT, culture and microscopy as reference tests and reported independently. The near-patient NAAT evaluation included testing a comprehensive selection of specimens: urine from men and endocervical swab, vaginal swab and urine from women.²⁴ Other evaluations included either men (urine) or women (cervical and/or vaginal swab) only.

Operational characteristics

The near-patient NAAT required three steps to perform, required electricity for operation and a temperature-controlled environment, with an objective result in an electronic format available in 90 min. In contrast, the ICTs and OIAs required nearly twice as many steps (5–7 steps) to perform, had a shorter time to result (25–40 min) and no power supply was required to perform the test. However, the ICTs and OIAs require good lighting and good vision on the part of the operator as subjective visual interpretation of the presence or absence of a control and test line is required to determine the result and there is no permanent record.

Performance

The near-patient NAAT had the highest sensitivities (>95%), with almost 100% specificities, consistently across all specimen types and both sexes.²⁴ When compared with laboratory-based NAATs as the reference tests, among the ICTs and OIAs, sensitivities ranged from 12.5% with the ACON Duo test²⁵ to 100% with the BioStar test; however, this study only included 5 NG-positive men (of 52 men in total).²² Figure 1 highlights the range of sensitivities and CIs of those POCTs. Specificities ranged from 89% to 99.8% for the ICTs and OIAs tests. One test (Binax Now) was evaluated among urine of symptomatic men and only compared with culture, no longer the accepted gold standard reference comparison.²³

Four POCTs (compared with laboratory-based NAATs) were evaluated using cervical swabs; GeneXpert CT/NG (sensitivity=100%, specificity=100%), GC check (sensitivity=70%, specificity=97%), BioStar OIA GC (sensitivity=60%, specificity=89%), ACON NG Duo (sensitivity=12.5%,

specificity=99.8%) and two using vaginal swabs; GeneXpert (sensitivity=100%, specificity=99.9%) and GC check (sensitivity=54%, specificity=98%). Only the GeneXpert CT/NG and BioStar OIA were evaluated using urine; with a sensitivity of 95.6% (females) and 98.0% (males) and specificity of 99.9% (males and females) for GeneXpert CT/NG; and sensitivity of 100% and specificity of 90% for BioStar, respectively (table 3).

DISCUSSION

This synthesis of two comprehensive systematic reviews included only six published papers relating to POCTs for NG, reporting on a total of six tests: four ICTs, one OIA and one near-patient NAAT-based test. Most studies were conducted in highly symptomatic key populations and among either men or women, not both. All but two evaluations^{21 23} were compared with laboratory-based reference NAATs, the current gold standard reference diagnostic test. The sensitivities of the ICTs/OIAs varied from 12.5% to 100% and specificities were >97%. As highlighted in table 3, some of the studies had small sample sizes and small numbers of gonococcal infections, resulting in large CIs around the point estimates of sensitivity and specificity.^{22 25} All ICTs/OIAs required five or more steps to perform the test and took between 25 and 40 min for a result, excluding any specimen preparation time. By contrast the near-patient NAAT had very high sensitivities (>95%) and specificities (≥99.9%) across specimen type and gender, required three steps to perform the test, minimal specimen preparation with results available in 90 min.

Until recently, commercially available POCTs for NG were mainly single antigen detection, as either a lateral flow ICT strip or OIA. As shown in this review, the majority of these tests had unacceptable sensitivity and required significant number of steps to perform and subjective visual interpretation, limiting their user-friendliness and compliance with the ASSURED criteria. Of the two ICTs reported, both (GC Check¹ and the NOW GC³) are no longer commercially available. As shown in the review, most evaluations of ICT or OIA NG POCTs were conducted using cervical or vaginal swabs, despite urine being a commonly collected sample, particularly for screening. In a field study by Causer *et al*²⁶ not included in these two systematic reviews, another NG ICT (Gonorrhoea Card Test, Immuno-Diagnostics, Foster City, California, USA) was evaluated using urines collected through community screening (men and women, n=29), with a sensitivity 66.7% (12.5–98.2). Although the time to results was 15 min, combined with specimen preparation which required centrifugation as routinely collected urine specimens were used, the total time to result from time of collection was ~33 min.

Table 2 Study characteristics and performance of point-of-care tests (POCTs) for *Neisseria gonorrhoeae*

Country	Study population	Symptoms (%)	Sex	Sample size (n)	POCT brand name	Gold standard	Gonorrhoea prevalence (%)	Specimen type	Time to result/ (# steps)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Reference
Benin	Sex workers	5.4	F	1084	GC check (PATH)	NAAT Amplicor CT/NG (Roche), location not specified	4.6	Cervical swab/vaginal swab	25 min (five steps)	70 (55 to 82)/54 (37 to 71)	97 (96 to 98)/98 (97 to 99)	55 (50 to 76)/61 (42 to 76)	98.7 (98 to 99)*/97.7 (96 to 99)*	Alary <i>et al</i> ¹⁰
Brazil	STI clinic attendees	High risk†	F	326	BioStar GC (OIA) (ThermoFisher Scientific)	Culture Modified Thayer-Martin	15.0	Cervical swab	25–40 min (seven steps)	60 (46 to 74)	89 (86 to 94)	56 (42 to 69)	92.6 (89.5 to 95.7)	Benzaken <i>et al</i> ²¹
Columbia	Sexually active 14–49 years, pregnant women excluded	100	F	491	ACON NG Duo test ImmunoAssay	Cobas Amplicor (Roche)	1.4	Endocervical swab		12.5 (0 to 41.7)	99.8 (99.3 to 100)	60.4	0.4	Nunez-Foreiro <i>et al</i> ²⁵
	Sexually active 14–49 years, pregnant women excluded	100	F	773	ACON NG Individual test ImmunoAssay	Cobas Amplicor (Roche)	1.4	Endocervical swab	No information	Not quantifiable	97.2 (96 to 98.5)	Not quantifiable	Not quantifiable	Nunez-Foreiro <i>et al</i> ²⁵
UK	Sexual health clinic attendees	67	M	52	BioStar OIA GC (BioStar)	Apitima Combo 2 assay	10	Urine	No information	100 (57 to 100)	98 (98 to 100)	83 (44 to 97)	100 (92 to 100)	Samarawickrama <i>et al</i> ²²
	Sexual health clinic attendees	67	M	33	BioStar OIA GC (BioStar)	Microscopy	12	Urine	No information	100 (51 to 100)	93 (78 to 98)	67 (30 to 90)	100 (88 to 100)	Samarawickrama <i>et al</i> ²²
	Sexual health clinic attendees	67	M	32	BioStar OIA GC (BioStar)	Culture	13	Urine	No information	100 (51 to 100)	93 (77 to 98)	67 (30 to 90)	100 (87 to 100)	Samarawickrama <i>et al</i> ²²
Japan	Urology department	100	M	58	Binax Now Gonorrhoea Test (Inverness)	Culture Thayer-Martin	58.6	Urine	25 min (six steps)	94 (80 to 99)*	96 (79 to 100)*	97* (84 to 100)*	92 (75 to 98)	Suzuki <i>et al</i> ²³
USA	STD, OB/GYN, teen, public health or family planning clinics	27	F	1722	GeneXpert CT/NG (Cepheid)	NAAT Apitima Combo 2 assay and ProbeTec ET system	1.3	Vaginal swab (self-collected)/endocervical swab	90 min (three steps)	100 (87.3 to 100)/100 (87.3 to 100)	99.9 (99.6 to 100)/100 (99.6 to 100)	91.7/100	100/100	Gaydos <i>et al</i> ²⁴
	STD, OB/GYN, teen, public health or family planning clinics	27	F	1722	GeneXpert CT/NG (Cepheid)	NAAT Apitima Combo 2 assay and ProbeTec ET system	1.3	Urine	90 min (three steps)	95.6 (78.1 to 99.9)	99.9 (99.7 to 100)	95.6	99.9	Gaydos <i>et al</i> ²⁴
	STD, OB/GYN, teen, public health or family planning clinics	27	M	1387	GeneXpert CT/NG (Cepheid)	NAAT Apitima Combo 2 assay and ProbeTec ET system	3.6	Urine	90 min (three steps)	98.0 (88.4 to 99.9)	99.9 (99.6 to 100)	98.0	99.9	Gaydos <i>et al</i> ²⁴

* Calculated by author (Watchis-Smith).¹⁷

† Referred by sexual partner or symptomatic.

F, female; M, male; NAAT, nucleic acid amplification technology; NPV, negative predictive value; OB/GYN, obstetrics/gynaecology clinics; OIA, optical immunoassay; PPV, positive predictive value.

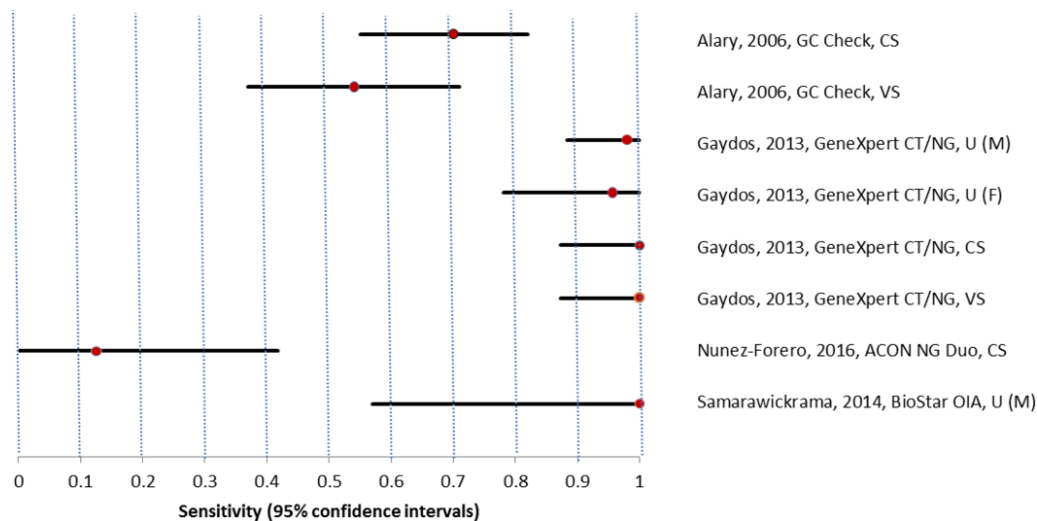


Figure 1 Comparison of sensitivities of *Neisseria gonorrhoeae* point-of-care tests compared with nucleic acid amplification technologies. CS, endo/cervical swab; F, female; M, male; U, urine; VS, vaginal swab.

For POCTs based on single antigen detection to be able to be used routinely, two major enhancements are needed: (1) further developmental research to increase their sensitivity and (2) modification to processes to reduce the number of steps.

Recent technological advances have resulted in the development of new NAAT-based assays with performance characteristics similar to those of the reference laboratory NAATs. Recent field testing of this CT/NG assay in remote primary health services in Australia has demonstrated its feasibility and high operational performance in a clinical primary care setting.^{26,27} Pilot studies have also been conducted in antenatal settings in Papua New Guinea and Botswana with the GeneXpert CT/NG test integrated into the antenatal pathway, with nearly all women agreeing to be tested, and for those who were positive, all were treated; 80%–100% of them on the same day, despite the 90 min wait for results.^{13,28} Although the electricity requirement for the GeneXpert CT/NG assay may limit its use for some community-based screening and immediate treatment, the assay could still improve access to and delivery of more timely results as specimens can be easily collected and transported for testing to the nearest suitable location with a source of electricity to power the test. Furthermore, this limitation related to power supply should be overcome by the new portable, battery-powered GeneXpert Omni device. A further advantage of the GeneXpert test not addressed at all with ICTs is the incorporation of two

NG targets, minimising the chance of false positive results with a commensal *Neisseria* species. This essentially equates to a ‘screen and confirm’ approach as would be routine practice in a laboratory setting. Also the GeneXpert is a dual test, which incorporates a simultaneous CT detection assay within the same test cartridge.²⁶ Very little data are available regarding the performance of any NG POCT for use with extragenital samples.

A number of novel rapid POC molecular platforms for detection of NG and CT are in the pipeline, which might become exceedingly valuable. However, due to the increasing antimicrobial resistance in NG, a POCT that provides a diagnostic result simultaneously with antibiotic resistance information would be ideal. The feasibility and accuracy of NAATs to determine antimicrobial resistance has been reported recently.²⁹ Such a test would provide LMICs with antimicrobial resistance data which had previously been limited and also enable individualised treatment, allowing recycling of antibiotics such as ciprofloxacin in areas where ceftriaxone treatment is recommended.³⁰

In summary, prior to August 2015, there have been very few published evaluations of POCTs for NG. Among the six identified, the majority demonstrated sensitivities and specificities too low to support routine use for screening and case finding. The new NAAT-based near-patient test had acceptable performance to be used for routine testing, and also with fewer steps to perform a test. From the pilot field studies in a number of

Table 3 Sensitivities and specificities of *Neisseria gonorrhoeae* point-of-care tests compared with nucleic acid amplification technology (NAAT) by specimen type

Specimen	Test	Number	Positive NAAT	Sensitivity (%)	95% CI	Negative NAAT	Specificity (%)	95% CI
Urine								
Male	GeneXpert CT/NG	1387	50	98.0	88.4 to 99.9	1336	99.9	99.6 to 100
	BioStar	52	5	100	57 to 100	47	98	98 to 100
Female	GeneXpert	1722	23	95.6	78.1 to 99.9	1695	99.9	99.7 to 100
Swab								
Cervical	GeneXpert CT/NG	1722	22	100	87.3 to 100	1688	100	99.8 to 100
	GC check	1084	50	70	55 to 82	1034	97	96 to 98
	ACON NG Duo	491	8	12.5	0 to 41.7	483	99.8	99.3 to 100
Vaginal	GeneXpert CT/NG	1722	22	100	87.3 to 100	1691	99.9	99.6 to 100
	GC check	1084	50	54	37 to 71	1034	98	97 to 99

settings, acceptability of the NAAT-based test is high, but further implementation research is warranted. We did not compare the cost of the assays as some POCTs are no longer commercially available and for others the market price for LMICs is not known. To truly increase uptake of NG POCTs to reduce disease burden worldwide, we need strong evidence of cost-effectiveness in LMICs to invest in POC testing, which should inform guidelines and ultimately stimulate development of new tests, increase demand and thereby reduce costs.

Key messages

- ▶ *Neisseria gonorrhoeae* point-of-care tests based on antigen detection lack sensitivity for screening, require 5–7 steps and results are available in 25–40 min.
- ▶ Near-patient nucleic acid amplification technologies have acceptable performance with fewer steps, but need electricity and have a turnaround time of 90 min.
- ▶ Strong evidence of cost-effectiveness is needed to inform guidelines and increase investment in test development, demand and reduce costs.

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