Multiplexed rapid technologies for sexually transmitted infections: a systematic review

Angela Karellis, Faheel Naeem, Suma Nair, Sneha D Mallya, Jean-Pierre Routy, Jacqueline Gahagan, Cédric P Yansouni, John Kim, Nitika Pant Pai

Multiplexed technologies for sexually transmitted infections offer a convenient diagnostics option to screen, confirm, and treat multiple pathogens simultaneously. Due to scarce published real-world diagnostic performance data, we did a systematic review. Two reviewers searched major databases for data published between Jan 1, 2009, and April 20, 2020, and abstracted and analysed sensitivity and specificity data from 24 studies, which assessed 17 multiplex rapid nucleic acid amplification test platforms and seven multiplex immunochromatographic devices. Overall, these studies evaluated 19 sexually transmitted infections in 26126 individuals. High sensitivity and specificity were shown for rapid nucleic acid amplification platform tests and immunochromatographic devices, with performance varying by pathogen, device, seropositivity, and subpopulation screened. As most devices yielded more than 95% sensitivity and specificity, immunochromatographic tests and rapid nucleic acid amplification test platforms can be advised for screening and confirmatory use. These highly accurate devices are appropriate for integrated, rapid screening initiatives for sexually transmitted infections to screen and treat many of these infections simultaneously, for antimicrobial stewardship, and for disease elimination programmes.

Introduction

According to WHO, more than 1 million new sexually transmitted infections are acquired every day, leading to a high clinical and socioeconomic burden, both for patients and society. Since the 1980s, WHO has recommended syndromic management to combat the influx of bacterial and viral sexually transmitted infections. Despite the increased popularity of this approach over the past several years, in 2021, regular screening for co-infections among key at-risk populations is needed to enable early diagnosis and optimal management. Although many screening approaches exist, the conventional diagnostic method entails the collection of samples from individuals for laboratory-based testing to produce results in a matter of days. This technique is considered the gold standard to detect sexually transmitted infections, but the use of this method is associated with several disadvantages. The joint COVID-19 and sexually transmitted infection screening initiatives have improved rapid testing, allowing same-day results, which complement laboratory testing in the spectrum of diagnostic care. Besides, antimicrobial stewardship is increasing as countries fight to combat resistant organisms. As such, exploring technologies and solutions to allow individuals to get tested and obtain their results in a single patient visit becomes pertinent.

Multiplexed rapid testing addresses several issues simultaneously by: reducing the number of visits to test for sexually transmitted infections thereby decreasing stigma, discrimination, and anxiety associated with frequent and multiple clinic visits; the burden of coordinating multiple patient appointments and tests; and loss of patients to follow-up. Multiplexed rapid testing further addresses issues related to routine testing’s high cost and low access.

Also, as several sexually transmitted infections share common transmission routes, at-risk individuals have an increased risk of acquiring many sexually transmitted infections, particularly as certain infections, such as syphilis, predispose the development of HIV infection. As such, we decided to explore multiplex rapid testing; this form of assessment simultaneously tests for several pathogens in a single assay while obtaining results with a rapid turnaround time. When the world is facing the COVID-19 pandemic, so as to avoid the neglect of routine screening, the importance of multiplex rapid testing is mounting.

To accommodate the needs of these various settings, two rapid testing options can screen for multiple sexually transmitted infections: immunochromatographic point-of-care tests and rapid nucleic acid amplification test (RNAAT) platforms. Immunochromatographic devices are handheld tests that detect host antibodies, whereas RNAAT platforms are larger bench-top devices, which can perform molecular testing to detect pathogens directly.

To the best of our knowledge, no systematic review provides insights on real-world comparative diagnostic accuracy to aid decision makers in selecting the appropriate test for their setting. To fill this knowledge gap, we reviewed the diagnostic performance of multiplex RNAAT platforms and multiplex immunochromatographic tests to evaluate which are best suited for rapid, simultaneous, multiple screening for sexually transmitted infections and for integrated screening, antimicrobial stewardship, and disease elimination of these key pathogens.

Methods

Search strategy and selection criteria

AK and FN independently evaluated articles in any language published on MEDLINE (via PubMed) and Embase between Jan 1, 2009, and April 20, 2020, for eligibility. They also screened bibliographies in relevant primary studies and review articles. All discrepancies were discussed and resolved between them and by discussion with a senior reviewer (NPP). The population, intervention, comparison, and outcome were defined and pre-specified.

Correspondence to: Dr Nitika Pant Pai, Department of Medicine, Faculty of Medicine, McGill University, Montreal, QC, Canada (nitika.pai@mcgill.ca)
Comparator, and outcomes strategy is presented in the appendix (p 1). Keywords used in the search string included multiplex*, duplex*, triplex*, quadruplex*, simultaneous*, point-of-care, rapid, platform, molecular, sexually transmitted infection*, and sexually transmitted disease*.

We included all observational studies or randomised controlled trials in clinical care including human participants tested with a commercialised multiplex rapid immunochromatographic test or RNAAT platform. Case series, case reports, and studies that used pre-collected specimens were excluded. We specified infections (HIV, acquired immunodeficiency syndrome, chlamydia, gonorrhea*, hepatitis, syphilis, Treponema pallidum, human papillomavirus, herpes simplex, and trichomonas).

Data analysis

A prepiolated data abstraction form was developed in Excel. Variables abstracted were authors, year of publication, publication type (ie, paper or abstract), study design, funding source, country of study, all specimen type of sexually transmitted infections, type of technology (RNAAT or immunochromatographic), specific test, pathogens able to be detected by the specified test, reference test, population, and sample size. When possible, sensitivity and specificity results were collected by specimen; however, when studies pooled accuracy results by specimen type, these parameters were reported herein as in the publication (appendix p 1).

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to critically appraise studies reporting diagnostic accuracy.12,13 We also explored funding sources to assess potential risk of bias. The protocol detailing the method of this systematic review has been registered in the PROSPERO database (registration number CRD4202179218).14

Results

4440 citations were screened overall, of which 4417 were excluded; an additional eligible study was retrieved during a review of bibliographies (figure). Finally, 24 studies satisfying the predefined criteria were included in the final set. Of these included studies, a total of 26126 individual study participants were assessed. The study characteristics and populations are presented in table 1. There were nine studies (37·5%) from Europe, six (25·0%) from Africa, three (12·5%) from Asia, three (12·5%) from North America, two (8·3%) from South America, and one (4·2%) from Australia. By study design, all studies were observational (20 [83·3%] were cross-sectional, two [8·3%] were cohort studies, one [4·2%] was a case-control study, and one [4·2%] was unclear).

A major proportion of studies (n=17; 70·8%) evaluated RNAAT platforms, whereas the rest (n=7; 29·2%) evaluated immunochromatographic tests. RNAAT platforms assessed a vast array of pathogens: Chlamydia trachomatis (n=16; 64·0%), Neisseria gonorrhoeae (n=15; 62·5%), Mycoplasma genitalium (n=5; 20·8%), Trichomonas vaginalis (n=5; 20·8%), Ureaplasma urealyticum and Ureaplasma parvum (n=2; 8·3%), Mycoplasma hominis (n=2; 8·3%), and herpes simplex virus-2 (n=1; 4·2%). Pathogens screened solely by rapid immunochromatographic tests were hepatitis B (n=1; 4·2%), hepatitis C (n=2; 8·3%), HIV (n=6; 25·0%), and Treponema pallidum (n=5; 20·8%).

The populations and eligibility criteria for screening varied considerably between studies. Whereas certain studies classified their patient population on the basis of symptoms, such as symptomatic or paucisymptomatic patients, others included asymptomatic volunteers.15,18,34

Across numerous studies, study participants seeking regular screening for sexually transmitted infections, medical consultation, or a biological check-up, suspected
| Study design          | Sample size | Country       | Testing setting                        | Multiplexed test                                                                 | Sexually transmitted infections assessed                                                                 | Population                                                                 |
|----------------------|-------------|---------------|----------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Cross-sectional      | 202         | France        | Hospital laboratory                    | Anyplex II STI-7 Detection kit PCR (Seegene, Seoul, South Korea)                  | Chlamydia trachomatis, Neisseria gonorrhoea, Trichomonas vaginalis, Mycoplasma genitalium, Mycoplasma hominis, Ureaplasma urealyticum, and Ureaplasma parvum | Symptomatic and paucisymptomatic patients                                 |
| Cross-sectional      | 292         | Netherlands   | Remote laboratory                      | Siemens VERSANT kPCR (Tarrytown, NY, USA)                                        | C trachomatis and N gonorrhoea                                                                                   | NA                                                                       |
| Cross-sectional      | 198         | Australia     | Onsite (remote Australian areas) for rapid testing and laboratory for reference testing | GeneXpert CT/NG (Cepheid, Sunnyvale, CA, USA)                                     | C trachomatis and N gonorrhoea                                                                                   | Aboriginal populations                                                  |
| Cross-sectional      | 897         | South Korea   | Hospital laboratory                    | Anyplex II STI-7 Detection kit PCR; BD ProbeTec strand displacement amplification (Becton Dickinson, Sparks, MD, USA); AmpliSens PCR assay (InterLabService, Moscow, Russia); Mycoplasma IST 2 Kit (bioMérieux, Marcy l’Étoile, France); Seeplex PCR (Seegene, Seoul, South Korea) | C trachomatis, N gonorrhoea, T vaginalis, M genitalium, M hominis, U urealyticum, and U parvum | Symptomatic patients and asymptomatic volunteers                                                                   |
| Cross-sectional      | 1768        | Belgium       | NA                                     | 5-DiaMGTV multiplex diagenode kit (Diagenode, Liege, Belgium)                     | M genitalium, T vaginalis                                                                                                | Men who have sex with men                                                |
| Cross-sectional      | 267         | Spain         | Hospital laboratory                    | Anyplex II STI-7 Detection kit PCR                                                | C trachomatis, N gonorrhoea, T vaginalis, M genitalium, M hominis, U urealyticum, and U parvum                 | Individuals seeking care suspected of having a sexually transmitted and blood-borne infection, HIV-negative men who have sex with men |
| Cross-sectional      | 997         | China         | National and Abbott laboratories       | Abbott RealTime CT/NG (Des Plaines, IL, USA)                                      | C trachomatis and N gonorrhoea                                                                                   | Female sex workers                                                       |
| Cross-sectional      | 453         | France        | Sexually transmitted disease clinic    | Bio-Rad Dx CT/NG/MG (Hercules, CA, USA)                                           | C trachomatis, N gonorrhoea, and M genitalum                                                                   | Males and females attending a sexually transmitted and blood-borne infection clinic |
| Cross-sectional      | 51          | Belgium       | Hospital                               | Taqman Array Card (Thermo Fisher Scientific, Waltham, MA, USA)                    | C trachomatis, N gonorrhoea, M genitalium, and T vaginalis                                         | Men who have sex with men                                                |
| Cohort               | 247         | South Africa  | Clinic for rapid testing and laboratory for reference testing | GeneXpert CT/NG                                                                     | C trachomatis and N gonorrhoea                                                                                   | Women seeking syndromic care                                             |
| Cross-sectional      | 383         | Zimbabwe      | Laboratories (type unspecified)        | GeneXpert CT/NG                                                                     | C trachomatis and N gonorrhoea                                                                                   | Men and women with genital discharge syndrome                             |
| Case-control         | 242         | Rwanda        | Hospital laboratory                    | STDFinder (multiplex ligation-dependent probe amplification, PathoFinder, Maastricht, Netherlands) | C trachomatis, N gonorrhoea, T vaginalis, M genitalium, Treponema pallidum, and herpes simplex virus-1 and virus-2 | Women who are infertile                                                   |
| Cross-sectional      | 491         | Colombia      | Public health laboratory               | Acon Duo (Acon Laboratories, San Diego, CA, USA)                                 | C trachomatis and N gonorrhoea                                                                                   | Sexually active women aged 14–49 years with lower urinary tract infection symptoms |
| Cross-sectional      | 1261        | Sweden        | Hospital laboratory                    | AmpliSens PCR (Hologic, San Diego, CA, USA)                                       | C trachomatis, N gonorrhoea, M genitalium, and T vaginalis                                                     | Sexually transmitted and blood-borne infection clinic attendees           |
| Prospective cohort   | 955         | France        | University laboratory for reference testing (unspecified for rapid testing) | Bio-Rad Dx CT/NG/MG                                                               | C trachomatis, N gonorrhoea, M genitalium, and T vaginalis                                                     | Individuals who undergo sexually transmitted and blood-borne infection screening, medical consultation, or biological check-up |

(Table 1 continues on next page)
of having a sexually transmitted infection, women seeking syndromic care, or sexually active women aged 14–49 years presenting with lower urinary tract infection symptoms were included.\textsuperscript{18,19,21,25,27–18,19}

Many studies focused on key at-risk populations such as men who have sex with men, transgender populations, Aboriginal populations, people who inject drugs, women with at least two recent partners, female sex workers, and labourers who have paid for sex.\textsuperscript{7,18,21,24,26,32,33–17,18} Additional populations of interest included pregnant women, women who are infertile, and patients with genital ulcer disease (table 1).

Table 2 presents the diagnostic accuracy of all RNAAT platforms by pathogen, which covered a total of 19 infections. A total of 15 RNAAT platforms were included in the Review, able to detect eight sexually transmitted infections, of which seven pathogens were bacteria and one was a virus (table 2).

13 devices were able to detect C. trachomatis, and the tests with highest diagnostic accuracy were STDFinder (PathoFinder, Maastricht, Netherlands; vaginal),\textsuperscript{26} AmpliSens PCR (Hologic, San Diego, CA, USA; vaginal),\textsuperscript{28} Amplicell II STI-7 Detection kit PCR (Seegene, Seoul, South Korea; urine for male participants).\textsuperscript{22} Certain devices yielded 100·0% sensitivity with very high specificity, such as Aurora FLOW (Roche, Basel, Switzerland; pooled vaginal for female participants and urine [urethral], rectal, or throat for male participants).\textsuperscript{36} Siemens VERSANT kPCR (Tarrytown, NY, USA; urine),\textsuperscript{36} and Bio-Rad Dx CT/NG/MG (Hercules, CA, USA; female urine)\textsuperscript{36} with a perfect combination of sensitivity (100.0%) and specificity (100.0%; table 2).

Certain devices yielded 100.0% sensitivity with very high specificity, such as Aurora FLOW (Roche, Basel, Switzerland; pooled vaginal for female participants and urine [urethral], rectal, or throat for male participants).\textsuperscript{36} Siemens VERSANT kPCR (Tarrytown, NY, USA; urine),\textsuperscript{36} and Bio-Rad Dx CT/NG/MG (Hercules, CA, USA; female urine)\textsuperscript{36} with a perfect combination of sensitivity (100.0%) and specificity (100.0%; table 2).
Conversely, the tests with optimal specificity and lesser sensitivity included AmpliSens PCR (vaginal and urine or urine for female participants and urine for male participants),28 Abbott RealTime CT/NG (Des Plaines, IL, USA; cervical),21 Bio-Rad Dx CT/NG/MG (urogenital and anorectal),29 and Taqman Array Card (Thermo Fisher Scientific, Waltham, MA, USA; unknown specimen type).21

Notably, in the study by Le Roy and colleagues,22 no positive cases of *C trachomatis* were identified, limiting the ability to test the Bio-Rad Dx CT/NG/MG’s sensitivity with urethral samples. However, the specificity of this test was 100·0% (95% CI 64·5–100·0; table 2). Additional tests presented with varying accuracy, with sensitivities ranging between 30·5% (17·9–43·1) and 99·3% (96·1–99·9) and specificities between 97·8% (not available) and 99·8% (99·2–100·0).15,18,20,25,27,31

12 RNAAT platforms can identify *N gonorrhoeae*. Several studies showed tests with 100·0% sensitivity and specificity, such as AmpliSens PCR (pooled vaginal and...
### Index test

| Reference test | Specimen type | Sensitivity, % (95% CI) | Specificity, % (95% CI) |
|----------------|---------------|-------------------------|-------------------------|
| **Neisseria gonorrhoeae**
| Van der Pol et al (2016) 31 | BD Max CT/GC/TV (Becton Dickinson, Sparks, MD, USA) | Vaginal | 95.7 (93.8–97.6) | 99.2 (98.7–99.6) |
| Van der Pol et al (2016) 31 | BD Max CT/GC/TV | Endocervical | 95.7 (93.8–97.6) | 99.2 (98.7–99.6) |
| Van der Pol et al (2016) 31 | BD Max CT/GC/TV | Urine (female) | 91.5 (85.8–95.4) | 99.5 (99.1–99.8) |
| Van der Pol et al (2016) 31 | BD Max CT/GC/TV | Urine (male) | 96.1 (92.9–98.4) | 99.4 (98.4–99.8) |
| Muvunjii et al (2011) 11 A | STD Finder (multiplex ligation-dependent probe amplification; PathoFinder, Maastricht, Netherlands) | Abbott RealTime CT/NG assay and gene-probe Aptima Combo 2 assay | Vaginal | 100.0 (56.1–100.0) | 100.0 (98.0–100.0) |
| Lorea et al (2018) 31 | Taqman Array Card (Thermo Fisher Scientific, Waltham, MA, USA) | NA | 75.0 (35.6–95.5) | 100.0 (89.8–100.0) |

### Neisseria gonorrhoeae

| Reference test | Specimen type | Sensitivity, % (95% CI) | Specificity, % (95% CI) |
|----------------|---------------|-------------------------|-------------------------|
| Rumyantseva et al (2015) 32 A | AmpliSens PCR | Vaginal and urine (female) and urine (male) | 100.0 (40.2–100.0) | 100.0 (99.7–100.0) |
| Rumyantseva et al (2015) 32 A | AmpliSens PCR | Vaginal | NA | 100.0 (98.2–100.0) |
| Rumyantseva et al (2015) 32 A | AmpliSens PCR | Urine (female) | 100.0 (19.3–100.0) | 100.0 (99.2–100.0) |
| Rumyantseva et al (2015) 32 A | AmpliSens PCR | Urine (male) | 100.0 (19.3–100.0) | 100.0 (99.2–100.0) |
| Bençot et al (2015) 31 A | Anyplex II STI-7 Detection kit PCR | Urine, endocervical, vaginal, and pelvic fluid | 100.0 (86.0–94.0) | 98.4 (NA) |
| Choe et al (2013) 31 A | Anyplex II STI-7 Detection kit PCR | Laboratory tests | 100.0 (100.0–100.0) | 99.2 (98.6–99.8) |
| Choe et al (2013) 31 A | Seeplex PCR | Laboratory tests | 100.0 (100.0–100.0) | 99.7 (99.3–100.0) |
| Choe et al (2013) 31 A | BD ProbeTec strand displacement amplification | Laboratory tests | 88.9 (76.6–100.0) | 99.9 (97.1–100.0) |
| Fernández et al (2016) 20 A | Anyplex II STI-7 Detection kit PCR | Abbott RealTime CT/NG | 100.0 (31.0–100.0) | 100.0 (87.1–100.0) |
| Fernández et al (2016) 20 A | Anyplex II STI-7 Detection kit PCR | Abbott RealTime CT/NG | 100.0 (51.7–100.0) | 100.0 (95.4–100.0) |
| Fernández et al (2016) 20 A | Anyplex II STI-7 Detection kit PCR | Abbott RealTime CT/NG | 88.9 (63.9–98.1) | 100.0 (86.3–100.0) |
| Fernández et al (2016) 20 A | Anyplex II STI-7 Detection kit PCR | Abbott RealTime CT/NG | 100.0 (62.9–100.0) | 100.0 (62.9–100.0) |
| Han et al (2014) 21 A | Abbott RealTime CT/NG | Roche Cobas Amplicor CT/NG and Qiagen care CT PCR assay | Cervical | 95.5 (75.1–99.8) | 99.9 (99.3–100.0) |
| Cauer et al (2015) 31 G | GeneXpert CT/NG | Cobas 4800 CT/NG test or Aptima Combo 2 assay | Urine | 100.0 (96.5–100.0) | 100.0 (97.5–100.0) |
| Mitchel et al (2017) 21 A | GeneXpert CT/NG | Anyplex II STI-7 and fast track diagnostic STD9 | Vaginal | 100.0 (NA) | 99.6 (NA) |
| Munganti et al (2015) 21 A | GeneXpert CT/NG | ProbeTecTM/multiplex PCR | Vaginal (female) and urine (male) | 97.8 (94.1–99.3) | 98.5 (95.3–99.6) |
| Bongaerts et al (2011) 21 A | Siemens VERSANT kPCR | BD ProbeTec ET System | Urine | 100.0 (66.3–100.0) | 100.0 (98.0–100.0) |
| Le Roy et al (2012) 21 A | Bio-Rad Dx CT/NG/MG | Culture | Urine, vaginal, endocervical, and urethral | 100.0 (NA) | 100.0 (NA) |
| Sednaoui et al (2011) 21 A | Bio-Rad Dx CT/NG/MG | Culture | Urogenital and anorectal | 100.0 (85.9–100.0) | 99.7 (98.8–99.9) |
| Nuñez-Foero and et al (2016) 21 A | Bio-Rad Dx CT/NG/MG | Laboratory tests | Endocervical | 12.5 (0.0–41.7) | 99.8 (99.3–100.0) |
| Van der Pol et al (2016) 31 A | BD Max CT/GC/TV | BD ProbeTec NG Q, Aptima Combo 2, and BD ProbeTec CT/GC assay | Endocervical | 95.5 (84.9–98.7) | 99.9 (99.7–100.0) |
| Van der Pol et al (2016) 31 A | BD Max CT/GC/TV | BD ProbeTec NG Q, Aptima Combo 2, and BD ProbeTec CT/GC assay | Urine (female) | 95.7 (85.5–98.8) | 99.7 (99.4–99.9) |

(Table 2 continues on next page)
| Index test | Reference test | Specimen type | Sensitivity, % (95% CI) | Specificity, % (95% CI) |
|------------|----------------|---------------|-------------------------|-------------------------|
| Van der Pol et al (2016) | BD Max CT/GC/TV | BD ProbeTec NG Q, Aptima Combo 2, and BD ProbeTec CT/GC assay | Urine (male) | 99.1 (94.9–99.8) 100.0 (99.5–100.0) |
| Muvunyi et al (2011) | STDFinder (multiplex ligation-dependent probe amplification) | Abbott RealTime CT/NG assay and gene-probe Aptima Combo 2 assay | Vaginal | 100.0 (65.5–100.0) 100.0 (98.0–100.0) |
| Lorea et al (2018) | Taqman Array Card | NA | NA | 85.7 (42.0–99.2) 93.2 (80.3–98.2) |
| Van der Pol et al (2016) | BD Max CT/GC/TV | Wet-prep microscopy or InPouch T vaginalis culture (BioMed Diagnostics, White City, OR, USA) and Aptima T vaginalis assay | Vaginal | 96.1 (91.7–98.2) 98.9 (98.0–99.4) |

**Mycoplasma genitalium**

| Index test | Reference test | Specimen type | Sensitivity, % (95% CI) | Specificity, % (95% CI) |
|------------|----------------|---------------|-------------------------|-------------------------|
| Choe et al (2013) | Anyplex II STI-7 Detection kit PCR | Laboratory tests | Urine and endocervical | 100.0 (100.0–100.0) 100.0 (100.0–100.0) |
| Choe et al (2013) | AmpliSens PCR | Laboratory tests | Urine and endocervical | 100.0 (100.0–100.0) 99.3 (98.7–99.9) |
| Choe et al (2013) | Seeplex PCR | Laboratory tests | Urine and endocervical | 91.7 (80.7–100.0) 99.8 (99.5–100.0) |
| Rumyantseva et al (2015) | AmpliSens PCR | Aptima Combo 2 assay | Vaginal | 81.9 (70.7–89.7) 100.0 (99.6–100.0) |
| Rumyantseva et al (2015) | AmpliSens PCR | Aptima Combo 2 assay | Vaginal | 76.5 (64.2–93.0) 100.0 (99.3–100.0) |
| Rumyantseva et al (2015) | AmpliSens PCR | Aptima Combo 2 assay | Urethral | 84.6 (65.9–95.1) 100.0 (99.9–100.0) |
| Rumyantseva et al (2015) | AmpliSens PCR | Aptima Combo 2 assay | pharyngeal | 91.5 (86.9–98.5) 99.2 (98.4–99.7) |
| De Baetselier et al (2017) | S-DiaMGTV multiplex diagenode kit (Diagenode, Liege, Belgium) | Real-time PCR | Vaginal | 91.5 (85.4–95.7) 99.7 (99.1–99.9) |
| De Baetselier et al (2017) | S-DiaMGTV multiplex diagenode kit | Real-time PCR | pharyngeal | 87.0 (73.7–95.1) 99.7 (99.1–99.9) |
| De Baetselier et al (2017) | S-DiaMGTV multiplex diagenode kit | Real-time PCR | Anorectal | 94.7 (86.9–98.5) 99.2 (98.4–99.7) |
| De Baetselier et al (2017) | S-DiaMGTV multiplex diagenode kit | Real-time PCR | pharyngeal | 88.9 (51.8–99.7) 99.7 (99.1–99.9) |

**Trichomonas vaginalis**

| Index test | Reference test | Specimen type | Sensitivity, % (95% CI) | Specificity, % (95% CI) |
|------------|----------------|---------------|-------------------------|-------------------------|
| Choe et al (2013) | Anyplex II STI-7 Detection kit PCR | Laboratory tests | Urine and endocervical | 100.0 (100.0–100.0) 99.3 (99.1–100.0) |
| Choe et al (2013) | Seeplex PCR | Laboratory tests | Urine and endocervical | 100.0 (100.0–100.0) 99.3 (99.1–100.0) |
| Fernández et al (2016) | AmpliSens PCR | Culture | Urine | 93.9 (78.4–98.9) 96.0 (73.1–99.7) |
| Rumyantseva et al (2015) | AmpliSens PCR | Aptima Combo 2 assay and Aptima T vaginalis assay | Vaginal | 100.0 (16.5–100.0) 100.0 (99.1–100.0) |
| Rumyantseva et al (2015) | AmpliSens PCR | Aptima Combo 2 assay and Aptima T vaginalis assay | pharyngeal | 91.5 (86.7–98.9) 99.9 (98.7–100.0) |
| Rumyantseva et al (2015) | AmpliSens PCR | Aptima Combo 2 assay and Aptima T vaginalis assay | Anorectal | 81.0 (65.7–94.1) 100.0 (99.6–100.0) |
| Rumyantseva et al (2015) | AmpliSens PCR | Aptima Combo 2 assay and Aptima T vaginalis assay | Urine (male) | 84.6 (78.0–91.0) 100.0 (98.9–100.0) |
| Van der Pol et al (2016) | BD Max CT/GC/TV | Wet-prep microscopy or InPouch T vaginalis culture (BioMed Diagnostics, White City, OR, USA) and Aptima T vaginalis assay | Vaginal | 96.1 (91.7–98.2) 98.9 (98.0–99.4) |
| Van der Pol et al (2016) | BD Max CT/GC/TV | Wet-prep microscopy or InPouch T vaginalis culture and Aptima T vaginalis assay | Endocervical | 83.4 (85.5–97.6) 99.3 (98.5–99.7) |
| Van der Pol et al (2016) | BD Max CT/GC/TV | Wet-prep microscopy or InPouch T vaginalis culture and Aptima T vaginalis assay | pharyngeal | 92.9 (87.7–96.0) 99.3 (98.5–99.7) |
| Muvunyi et al (2011) | STDFinder (multiplex ligation-dependent probe amplification) | Microscopic evaluation and confirmed by PCR | Vaginal | 100.0 (84.0–100.0) 90.3 (85.3–93.8) |
Table 2: Diagnostic accuracy of rapid nucleic acid amplification test platform devices

| Index test | Reference test | Specimen type | Sensitivity, % (95% CI) | Specificity, % (95% CI) |
|------------|----------------|---------------|-------------------------|-------------------------|
| U urealyticum | Seeplex PCR | Laboratory tests | Urine and endocervical | 100.0 (100.0-100.0) | 99.4 (98.9–99.9) |
| T vaginalis | STDFinder (multiplex ligation-dependent probe amplification) | Argene real-time PCR and Abbott RealTime HSV1/2 | Vaginal | 100.0 (51.7–100.0) | 95.2 (92.6–98.1) |

NA=not available. *Diagnostic accuracy to detect U urealyticum or U parvum.

100·0% sensitive and 99·4% specific. Although none yielded perfect diagnostic accuracy, the remaining tests observed present sensitivities between 92·9% (95% CI 87·7–96·0) and 96·1% (91·7–98·2) and specificities between 95·0% (73·1–99·7) and 99·3% (98·5–99·7; table 2).10

Three RNAAT platforms can detect U urealyticum, although none yielded perfect diagnostic accuracy. The Seeplex PCR (urine and endocervical) was 100·0% (95% CI 100·0–100·0) sensitive and 99·4% (98·9–99·9) specific.10 The Anyplex II STI-7 Detection kit PCR (urine and endocervical) showed 97·8% (94·8–100·0) sensitivity and 99·3% (98·7–99·9) specificity; whereas the Mycoplasma IST 2 Kit (bioMérieux, Marcy l’Etoile, France; urine and endocervical) showed 44·9% (36·6–53·2) sensitivity and...
The Anyplex II STI-7 Detection kit had a sensitivity of 70.0% (59.7–80.3) and specificity of 97.0% (not available). Although the Mycoplasma IST 2 Kit had low sensitivity (urine and endocervical), high specificity (99.7% [99.2–100.0]; table 2) was observed. Herpes simplex virus-2 could be identified by STDFinder (vaginal), which was associated with ideal sensitivity (100.0%) and a specificity of 96.2% (92.6–98.1) to detect this virus (table 2).

Table 3 shows the diagnostic accuracy of all rapid multiplexed immunochromatographic tests by pathogen. Nine immunochromatographic tests are included in our Review, which can identify four sexually transmitted
infections, one of which is a bacterial pathogen and three are viral pathogens.

To detect *T pallidum*, the sole bacterium detected by immunochromatographic tests, the SD Bioline HIV/Syphilis Duo Test (Standard Diagnostics, Giheung-gu, South Korea) was shown to have optimal diagnostic accuracy (for venous blood) in the study by Ormeling and colleagues, and 86.4% (95% CI 65.1–97.1) sensitivity and 100.0% (99.1–100.0) specificity in the study by Lodiongo and colleagues. Two additional studies showed moderate to high sensitivities and specificities with fingerstick blood. The INSTI Multiplex HIV-1/HIV-2/ syphilis antibody test kit (BioLytical, Richmond, BC, Canada) yielded suboptimal sensitivity (56.8% [44.7–68.2]) and high specificity (98.5% [95.7–99.7]; table 3).

For the detection of hepatitis B virus (table 3), the sole immunochromatographic test that could detect the virus was HIV/HCV/HBsAg Triplex (BioSynex, Strasbourg, France; blood), which yielded optimal diagnostic accuracy. Similar to hepatitis B virus values, the HIV/HCV/ HBsAg Triplex (blood) yielded ideal sensitivity and specificity. Two tests showed 100.0% specificity and variable sensitivity: MedMira HIV/HCV/HBV (whole blood) and MedMira HIV/HCV (whole blood). The remaining tests generally showed higher specificity than sensitivity. Sensitivities varied between 80.4% (95% CI 66.1–90.6) and 92.3% (88.4–96.2) and specificities between 85.3% (73.8–93.0) and 99.5% (98.9–100.0). HIV can be detected by three different immunochromatographic tests (table 3), two of which show 100.0% sensitivity and 100.0% specificity: SD Bioline HIV/Syphilis (BioLytical, Richmond, BC, Canada; fingerstick, serum blood, or venous blood) and HIV/HCV/HBsAg Triplex (BioLytical, Richmond, BC, Canada; blood). The SD Bioline HIV/Syphilis Duo Test (venous blood [plasma] or fingerstick blood) and the INSTI Multiplex HIV-1/HIV-2/ syphilis antibody test (fingerstick blood) were shown to yield optimal or near-optimal sensitivity and specificity.

The quality assessment as evaluated by the QUADAS-2 checklist is described in the appendix (pp 1–2). An important subset of questions showed positive answers for the majority of studies, including appropriate study design and use of a quality index and reference standard tests, among others. Furthermore, few studies exhibited evidence of introducing bias, although several studies presented limited information to definitively confirm absence of bias.

**Discussion**

Our Review consolidates all available literature published between Jan 1, 2009, and April 20, 2020, on rapid multiplex technologies (commercialised RNAAT platforms and immunochromatographic point-of-care multiplexed tests) able to detect at least two sexually transmitted infections simultaneously. To our knowledge, this evaluation is the first of its kind to assess the diagnostic accuracy in real-world settings (ie, point-of-care, near patient care, or in laboratory facilities).

A key trend observed was the overall high diagnostic performance as exhibited by both immunochromatographic tests and RNAAT platforms. With respect to sensitivity, 55.6% (ten of 18 entries) of immunochromatographic results and 65.7% (65 of 99) of RNAAT results, showed sensitivity values of at least 95%, spanning the various sexually transmitted infections examined. In fact, 38.9% (seven of 18) of immunochromatographic entries and 44.0% (44 of 99) of RNAAT entries showed 100.0% sensitivity. The majority of results showed high specificity as well: among RNAAT platforms, 45.0% (45 of 99) showed 100.0% specificity and 94.9% (94 of 99) were at least 95.0%; among immunochromatographic tests, 55.6% (ten of 18) showed perfect specificity and 100.0% (18 of 18) showed more than 95.0% specificity. This result alludes to the high benefit of immunochromatographic tests and RNAAT platforms during screening and for confirmatory purposes. Nearly all commercialised RNAAT platform devices yielded high diagnostic performance (for both sensitivity and specificity), as shown by several studies.

Moreover, certain high-throughput and low-throughput platforms consistently yielded high sensitivity and specificity for several sexually transmitted infections; these included the Anyplex II STI-7 Detection kit PCR, AmpliSens PCR, Bio-Rad Dx CT/NG/MG, HIV/HCV/HBsAg Triplex, STDFinder, Siemens VERSANT kPCR, and Cepheid’s GeneXpert. Among all immunochromatographic tests, the high performance of the SD Bioline HIV/Syphilis Duo Test stood out. In particular, the Anyplex II STI-7 Detection kit PCR, STDFinder, and AmpliSens PCR offer additional benefits in clinical care due to their ability to detect at least four sexually transmitted infections concurrently.

With respect to usefulness in diagnostic care, the majority of RNAAT platforms were used in laboratories. At or near the point of care, several investigators who led field-based studies expressed the clinical usefulness and high diagnostic accuracy of Cepheid’s GeneXpert low-throughput RNAAT platform device for use near patients, particularly to diagnose gonorrhoeae and chlamydia. Systematic review findings, including a 2014 evaluation done by the Pacific Northwest Evidence-based Practice Center, further support this statement. The device’s diagnostic performance in particular is a winning point: GeneXpert’s high sensitivity and specificity (both >97.0%) eliminates the need for confirmatory testing, allowing for a rapid triage of patients to treatment pathways, obviating losses to follow-up.

Rapid multiplexed immunochromatographic tests complement the usage of RNAAT platform testing and
might prove useful to fill timely access and screening gaps for simultaneous testing as shown in many studies done in diverse outpatient clinics or mobile units at or near the point of care. These tests are generally best suited for application in remote or low-resource areas at or near the point of care, although screening can also be done by rapid sample collection in the field followed by sample testing with an RNAAT platform at a centralised facility. Immunochromatographic tests do not require sophisticated laboratory techniques, thereby enabling their use in outreach settings. On the basis of the findings, we recommend that, before widespread implementation, health-care professionals and policy makers assess the needs of the populations who would undergo screening and the characteristics of their specific settings. We recommend that health-care professionals can use immunochromatographic tests, in particular for screening purposes, to reach populations in outreach settings and those who seek rapid HIV, hepatitis B, hepatitis C, and syphilis testing, whereas health-care professionals with access to platform testing can use RNAAT devices, especially for confirmation. In fact, a large number of RNAAT platforms able to detect HIV and hepatitis C virus are very useful in practice including in middle-income and high-income settings, which increase the speed and efficiency of diagnostic testing.

We observed that the performance of rapid immunochromatographic tests varied depending on several factors: (1) co-infection prevalence; (2) individuals screened and the eligibility or screening criteria used; (3) the interplay of various pathogens with the patient’s immune system; (4) many cofactors that contaminate diagnostic accuracy in the immunochromatographic test; and (5) algorithms used to evaluate index test performance. These factors played a role in the performance of rapid multiplexed RNAAT platforms to a lesser degree than in rapid immunochromatographic tests. In this Review, although we focused our evaluation of diagnostic accuracy by pathogen, type of device, specimen type, and population, decision makers could incorporate these additional factors to further aid the selection of appropriate diagnostic tools for their settings. For instance, the varying populations might attribute to the differing results as observed by Berço and colleagues and by Fernández and colleagues. The study by Berço and colleagues included symptomatic and paucisymptomatic patients whereas the study by Fernández and colleagues evaluated a more diverse patient population, including individuals seeking care suspected of having a sexually transmitted infection and HIV-negative men who have sex with men. More specifically, although the same index test (Anyplex II STI-7 Detection kit PCR) and reference test (Abbott RealTime CT/NG assay) were used in these studies, sensitivity (85-1% and 93-0-100-0%) and specificity (97-8% and 98-4-100-0%) values varied during the ongoing pandemic.

The results of this Review will allow decision makers to objectively select the appropriate test for use in accordance with devices’ diagnostic accuracy, most common sexually transmitted infections diagnosed in their setting, available clinical infrastructure, and testees’ preference of specimen collected.

Although some technologies showed perfect diagnostic accuracies (100-0% sensitivity and specificity), some of these results should be interpreted with caution. For instance, several studies were associated with wide CIs for select devices, such as the variable reference standard tests. Volunteer and selection bias (convenience sampling) were present and interpretation bias (limitation of human readers) can lead to false positive readings.

With RNAAT platforms, challenges observed were the ability to amplify, which impedes the capacity to
simultaneously detect multiple pathogens, due to the competition of various mix reactions or the use of non-specific interactions between primer and probes; the requirement of intensive labour to use RNAAT testing; and in a specific case, the inability of the Mycoplasma IST 2 Kit to distinguish between species of the *Mycoplasma* genus. Of note, as made evident by this Review, although RNAAT platforms are generally recognised as highly accurate tests (for both sensitivity and specificity) to screen and diagnose sexually transmitted infections, our findings showed that each infection is optimally detected by one type of multiplexed technology (RNAAT or immunochromatographic). Although we acknowledge that multiplex RNAAT platforms and immunochromatographic sexually transmitted infection tests complement each other well in settings outside the laboratory, this fact limits the testing capacity of some clinics to detect bacterial sexually transmitted infections, principally because costly infrastructure and training are required for RNAAT testing. However, of note, this Review solely included commercialised tests used in routine care. We excluded some studies that presented results associated with novel diagnostic rapid multiplexed technologies used outside routine diagnostic settings from our Review. In the event that some of these tests are to become commercialised in the future, pathogens such as *T. pallidum*, HIV, hepatitis A virus, hepatitis B virus, and human papillomavirus could be detected via RNAAT testing.

Overall, diagnostic performance varied by sexually transmitted infection, populations screened, prevalence and seropositivity, reference standards that varied in settings (immunochromatographic and RNAAT), and type of technology. As a result, we conclude that the majority of commercialised immunochromatographic tests and RNAAT platforms are suitable for both screening and confirmatory purposes. Nonetheless, due to device-specific features, such as portability and the requirement of infrastructure, immunochromatographic tests might be best suited for initial screening and high-throughput RNAAT platforms for confirmatory testing. Combining benefits of clinical usefulness and high diagnostic accuracy, promising platform technologies are useful for both point-of-care screening and diagnosis.

In alignment with international and national sexually transmitted infection disease agendas, rapid multiplexed RNAAT molecular platforms are ready for deployment in integrated sexually transmitted infection screening initiatives. Although immunochromatographic tests are suitable to screen for HIV, hepatitis C virus, and syphilis, there is an urgent need to develop rapid multiplex point-of-care devices for chlamydia, gonorrhoea, and human papillomavirus. Regardless, due to the high feasibility and high accuracy shown, both rapid multiplexed technologies offer immense potential to complement traditional testing in the detection of several pathogens simultaneously. These devices can also have an impact in low-resource settings, further adding value on access and expanded testing to reach, screen, and link undiagnosed populations to care and prevention pathways.

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