World Health Organization

GUIDELINES FOR THE MANAGEMENT OF SYMPTOMATIC SEXUALLY TRANSMITTED INFECTIONS

# **WEB ANNEX A.** SYNDROMIC MANAGEMENT OR POINT OF CARE TESTS FOR URETHRAL DISCHARGE: SYSTEMATIC REVIEW AND MATHEMATICAL MODELLING

JUNE 2021

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Guidelines for the management of symptomatic sexually transmitted infections: Web Annex A. Syndromic management or point of care tests for urethral discharge: systematic review and mathematical modelling

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# CONTENTS

# 1. INTRODUCTION

An estimated 340 million new cases of curable sexually transmitted infections (STIs) are diagnosed across the globe annually among men and women between the ages of 14 and 49 [1]. Due to their impact on many facets of health – from quality of life and fertility, to development of cancer and heightened susceptibility to HIV transmission - STIs are a worldwide concern.

In 2003, the World Health Organization (WHO) developed guidelines to aid clinicians in the syndromic management of patients with symptoms of STI, such as urethral discharge (Figures 1 and 2), vaginal discharge, lower abdominal pain and genital ulcers [2]. Syndromic management involves a cascade of decisions that have been organised into flowcharts or algorithms. Within each flowchart is a series of steps to determine whether someone presenting with a sign (clinically-observed indication of infection) or syndrome (symptoms identified by a patient) should be treated for a particular STI. Within a flowchart, there may be multiple steps, such as risk assessment, clinical examination, and the performance of tests. Although laboratory testing is optimal for STI diagnosis, in many settings such testing is unavailable. The syndromic approach is often used for STI management in resource-constrained settings where access to laboratory facilities, technical personnel, specific medicals tests, and/or transportation may be limited or non-existent, or where patient follow-up is unlikely or impossible.

By treating the organism(s) most commonly responsible for observed signs and symptoms by way of the urethral discharge flow chart, clinicians can treat a number of curable STIs, such as Neisseria gonorrhoeae (NG) and Chlamydia trachomatis (CT) [3]. However, management based on signs/symptoms alone can also lead to the unnecessary treatment of patients who do not have an STI – raising risks of antimicrobial resistance. Point of Care tests (POC) may be an alternative management strategy that could increase the appropriate treatment of men presenting urethral discharge, and potentially reduce unnecessary treatment.

The best evidence to determine the effects of syndromic management for urethral discharge is to review studies comparing the clinical outcomes of men who have been managed syndromically to men who have not been managed syndromically. We however, conducted a comprehensive search of multiple health databases for these types of studies and did not find any. In order to determine the effects, we therefore conducted this review and analyses to achieve three important objectives:

1. to determine the test accuracy of different flowcharts for the syndromic management of persistent and non-persistent urethral discharge to manage *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT) infections;
2. to model and present the impact of different flowcharts and point-of-care tests (PCOTs) on the identification of NG, and NG and CT; and
3. to model the risks of falsely treating men without NG, the related costs of the tests, and the costs of antimicrobial resistance.

**Figure 1.** Flowchart for the diagnosis of STIs in men presenting with urethral discharge, using history and risk assessment. [2]

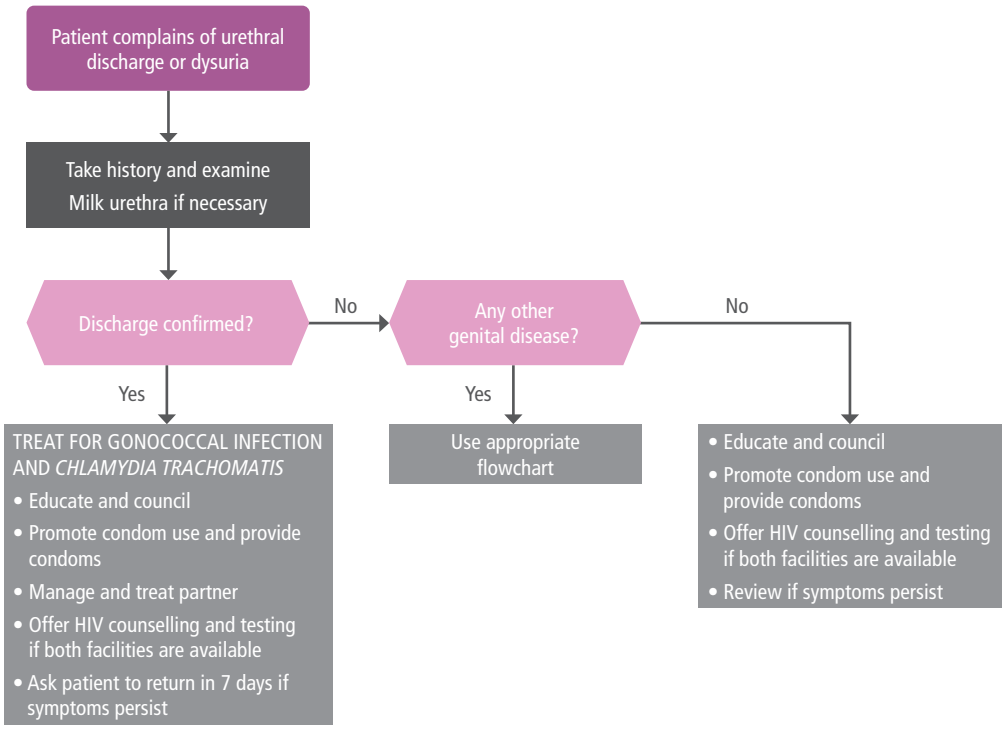
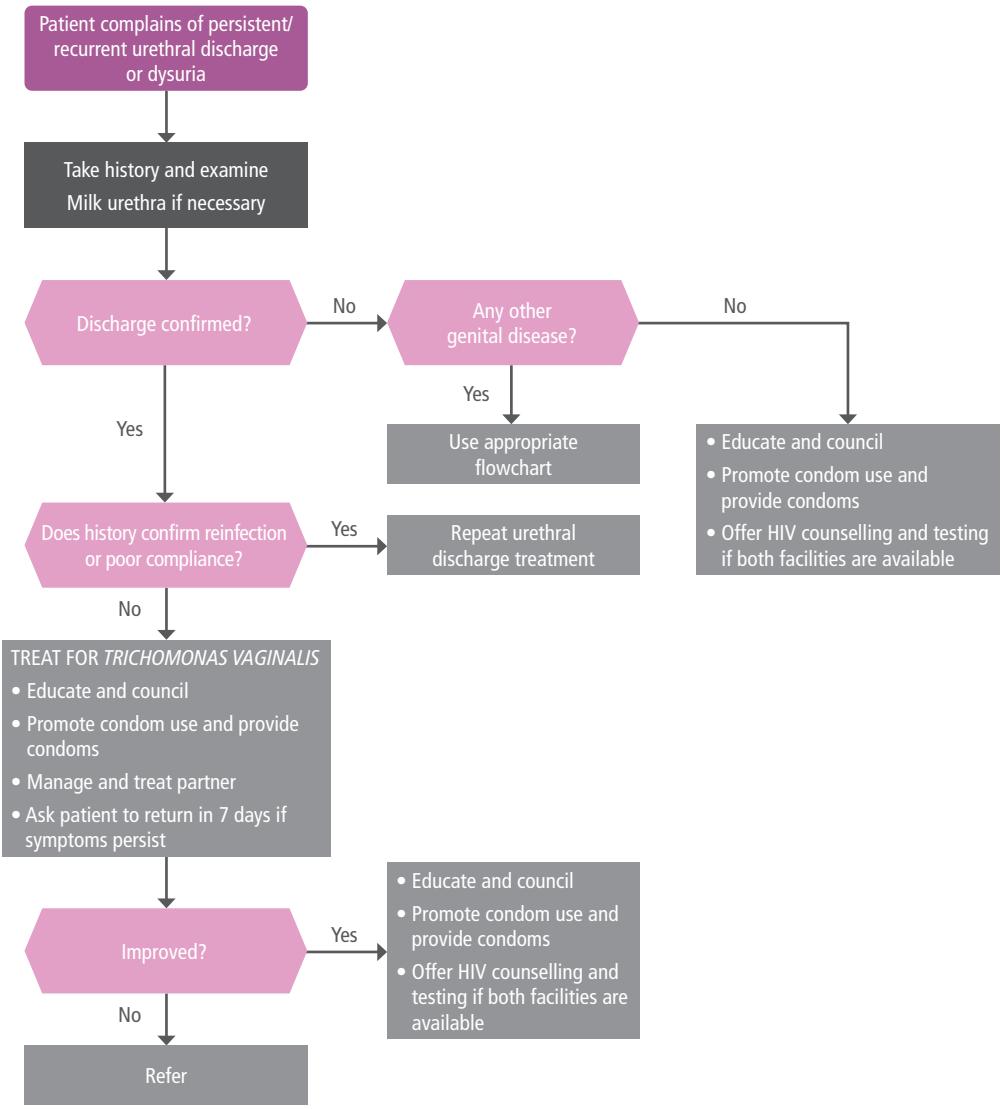


**Figure 2.** Flowchart for the diagnosis of STIs in men presenting with resistant or persistent urethral discharge, using history and risk assessment. [2]



# 2. METHODS

## Literature search

We conducted a systematic search of studies reporting on the test accuracy of flowcharts, published between 2000 (3 years before the publication of the WHO guideline) and February 2019 in OVID Medline and EMBASE. The search strategy is presented below.

Database: Embase <1974 to 2019 February 07>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to February 07, 2019>

Search Strategy:

1. Software Design/
2. flowcharts.mp.
3. Flowchart.mp.
4. algorithm.mp.
5. algorithms.mp.
6. flow charts.mp.
7. flow chart.mp.
8. clinical pathway.mp.
9. clinical pathways.mp.
10. risk*.mp.
11. syndromically.mp.
12. syndromic.mp.
13. signs.mp.
14. symptoms.mp.
15. symptom.mp.
16. exam*.mp.
17. swab*.mp.
18. (sensitiv* or specificity).mp. or predict*.tw. or diagnos*.mp. or di.xs.
19. "surveys and questionnaires"/ or (survey* or questionnaire*).ti,ab.
20. (associat* or correlat* or odds ratio or prevalen* or epidemiol*).ti,ab.
21. or/1-20
22. (gonoc* or gonorr* or chlamydia* or trich* or genitalium or mycoplasm* or Mgen).mp.
23. (urethr* or penis or penile).mp.
24. (discharge* or secrete* or secretion*).mp.
25. milk*.mp.
26. 23 and (24 or 25)
27. 21 and 22 and 26
28. limit 27 to yr="2000 -Current"
29. remove duplicates from 28

## Selection of studies and data abstraction

We included studies that evaluated the diagnostic accuracy and validation of urethral discharge flowcharts for *Neisseria gonorrhoeae* (NG) and/or *Chlamydia trachomatis* (CT) infections in men with urethral discharge (or persistent urethral discharge). We also searched for flowchart studies for *Mycoplasma genitalium* (MG) infections; however, we did not find any and therefore do not provide further details in this report.

We included studies reporting on the following flowcharts:

- Flowchart 1 (WHO algorithm 1) = history and risk assessment;
- Flowchart 2 (WHO algorithm 2) = history, risk assessment and genital examination (e.g., milking urethra);
- Flowchart 3 (WHO algorithm 3) = history, risk assessment, genital examination (e.g., milking urethra), and urethral discharge samples for Gram staining and microscopy.

Eligible studies assessed the diagnostic accuracy of flowcharts with laboratory tests as a gold standard to screen for the STIs, for example, nucleic acid amplification tests (NAATs) or polymerase chain reaction (PCR) for NG/CT, gram stain or culture for NG. Studies that presented data on sensitivity, specificity, positive predictive values (PPV), negative predictive value (NPV) or that provided data from which these parameters could be calculated using two by two tables were included (i.e., true positives/negatives and false positives/negatives). We excluded studies published in languages other than English, French, or Spanish. Two investigators assessed the studies for relevance by title and abstract, and assessed the full text of potentially relevant studies. In case of disagreement between the investigators, they discussed in order to reach consensus, but if it was not reached, they consulted another investigator. Data from the studies was abstracted by an investigator and verified by another investigator.

## Risk of bias of included studies

We assessed the risk of bias of the different studies using the QUADAS-2 assessment tool [4]. We assessed the risk of bias for patient selection, index test, reference standard, flow and timing as high, low or unclear.

Signaling questions for each domain of the QUADAS-2 tool are also listed below:

- Patient selection
  - Was a consecutive or random sample of patients enrolled?
  - Was a case–control design avoided?
  - Did the study avoid inappropriate exclusions?
- Index test
  - Were the index test results interpreted without knowledge of the results of the reference standard?
  - If a threshold was used, was it prespecified?
- Reference standard
  - Is the reference standard likely to correctly classify the target condition?
  - Were the reference standard results interpreted without knowledge of the results of the index test?
- Flow and timing
  - Was there an appropriate interval between index tests and reference standard?
  - Did all patients receive a reference standard?
  - Did all patients receive the same reference standard?
  - Were all patients included in the analysis?

## Statistical analysis

We conducted a meta-analysis by pooling the true positives/negatives and false positives/negatives from all studies within different types of flowcharts. We calculated the pooled sensitivity and specificity for the different type of the flowcharts using the WINPEPI software (version 11.65, August 2016). If the study had presented the results separately for NG or CT, the study with the higher PPV was included in the meta-analyses so as not to over represent any study.

To understand any differences in sensitivity and specificity, we explored the results according to the risk of bias of the included studies. We did not find that differences in the results could be explained by risk of bias and therefore do not present the analyses separately by risk of bias.

## Certainty of the evidence

We used the GRADE approach to assess the certainty of the evidence for the diagnostic accuracy of the tests by considering the GRADE domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias (https://gdt.gradepro.org/app/handbook/handbook.html). We did not assess the certainty of the evidence for the results of the modelling which was based on multiple assumptions (see section below).

## Modelling of effects and costs of syndromic management

Using the pooled estimates of sensitivity and specificity, we modelled the effects and costs of syndromic management using the different flowcharts and point of care tests with different test accuracy. We first calculated the number of men who would miss treatment (due to false positives of the test) or would be falsely treated (due to false negatives of the test). We then calculated the costs of the flowcharts and point of care tests, and the costs if antimicrobial resistance developed. The mathematic model was developed and run using Excel.

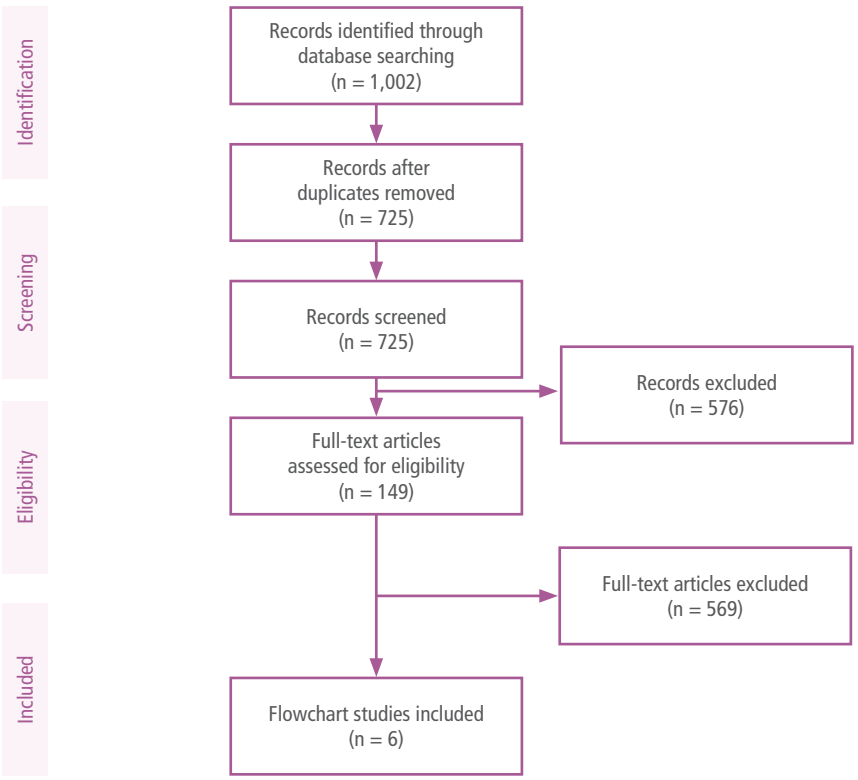
We made the following assumptions in the model based on current literature and hypotheses:

1. the prevalence of NG/CT in a population of men with urethral discharge is 10%, 40% or 60%; the prevalence of only NG in a population of men with urethral discharge is 5%, 20% or 30% (based on included studies);
2. when calculating the number of men with CT and NG, the number of true cases is distributed as 75% with CT and 25% with NG (based on included studies);
3. therapy for NG/CT with 1000 mg of azithromycin and ceftriaxone 250 mg delivered intramuscularly costs $1.66 USD; [5]
4. cure rates of CT and NG with treatment are 94% and 98% respectively, while adverse events are 15% and 3% for CT and NG respectively; [5]
5. potential sensitivity and specificity of point of care tests are 60% and 90%; 70% and 80%; 70% and 90%; 80% and 80%; 80% and 90%;
6. costs of administering flowcharts 1 and 2 is $0.00 USD, while administration of flowcharts 3 and 4 is $1.00 USD (typically with the use of gram stain/microscopy);
7. point of care tests cost $3.00 USD, while Genexpert costs $16.00 USD;
8. the cost of treatment when antibiotic resistance occurs is $25.00 USD for a new treatment (cure and adverse effects are similar to assumption #3); and,
9. long term consequences of missed treatment (e.g., repeat tests) are not calculated.

# 3. RESULTS

We found 1,002 citations and after removal of 277 duplicates, there were 725 citations for title and abstract screening. After excluding studies that were not relevant, we obtained and screened 148 full text articles. Six studies met our inclusion criteria and were included. See Figure 3 for the PRISMA diagramme for the flow of studies.

**Figure 3.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) flow diagram.




## Study characteristics

The six eligible studies [6-11] included a total of 1,570 participants. All studies evaluated flowcharts against reference tests for NG and/or CT. None of the studies specified whether participants had persistent or non-persistent urethral discharge. Most studies took place in Asia.

## Table 1. Study characteristics of all included studies

| Study | Country | Design | N | STI Prevalence | Setting | Population (age group) | Flowchart description(s) | Reference test(s) |
|---|---|---|---|---|---|---|---|---|
| Bhavsar 2014 | India | Cross-sectional | 17 | NG: 88.2 | Hospital Skin and VD outpatient department | General population men (15 – 70 years) | NACO 2 | NG: Gram stain |
| Chandeying 2000 | Thailand | Cross-sectional | 129 | NG 32.6;<br>CT 23.3; | STI units | General population men (mean/median age = 30 years) | WHO algorithm 2;<br>WHO algorithm 2 + microscopy; | NG: culture and/ or PCR<br>CT: PCR |
| Liu 2003 | China | Cross-sectional | 347 | NG: 61.1<br>CT: 23.6<br>NG/CT: 69.2 | STD clinics | General population men (18 – 83 years) | WHO algorithm 1 | NG/CT: PCR |
| Tsai 2008 | Taiwan, China | Cross-sectional | 335 | NG/CT: 40.6 | STD clinic, genitourinary outpatient clinic | General population men (17 – 50 years) | WHO algorithm 2 | NG/CT: PCR |
| Wang 2003 | China | Cross-sectional | 325 | NG: 64.3<br>CT: 16.3<br>NG/CT: 72.6 | Urban STD clinics | General population men (16 – 63 years) | WHO algorithm 3: history + risk assessment + genital examination + urethral discharge samples for Gram staining | NG: Gram stain + culture<br>CT: PCR |
| Yu 2005 | Taiwan, China | Cross-sectional | 307 | NG: 10.1<br>CT: 14.3 | STD Control Center clinic | General population men (16 – 50 years) | Taipei locally developed syndromic treatment guideline 2 | NG/CT: PCR<br>microscopy + culture |

CT: *Chlamydia trachomatis;* NACO: National AIDS Control Organization; NG: *Neisseria gonorrhoeae (NG)*; PCR: polymerase chain reaction; STI: sexually transmitted infection; STD: sexually transmitted disease; WHO: World Health Organization

## Risk of bias assessment

The studies were at low risk of bias for all domains of the QUADAS-2 tool. See Table 2 below for the assessment.

## Table 2. Risk of bias assessment for included studies

| Study | Patient Selection | Index Test | Reference Standard | Flow and Timing |
|---|---|---|---|---|
| Bhavsar 2014 | Low | Low | Low | Low |
| Chandeying 2000 | Low | Low | Low | Low |
| Liu 2003 | Low | Low | Low | Low |
| Tsai 2008 | Low | Low | Low | Low |
| Wang 2003 | Low | Low | Low | Low |
| Yu 2005 | Low | Low | Low | Low |

## Performance of urethral discharge flowcharts for *N. gonorrhoeae* (NG) and/or *C. trachomatis* (CT)

**Flowchart 1:**

Only one study [8] reported on the diagnostic accuracy of using history and risk assessment in men presenting with urethral discharge to manage NG and/or CT infections. Table 3 presents the performance of the flowcharts.

**Flowchart 2:**

Four studies [6, 7, 9, 11] reported on the diagnostic accuracy of using a genital examination in conjunction with history and risk assessment. Table 3 presents the performance of the flowcharts.

**Flowchart 3:**

Two studies [7, 10] assessed the accuracy of using an algorithm to manage NG and/or CT infections based on history, risk assessment, genital examination, and gram staining and microscopy for urethral discharge samples. There was sparse data to calculate the specificity of the flowchart in both studies. Table 3 presents the performance of the flowcharts.

**Flowchart 4:**

We found no studies that assessed other country specific flowcharts.

## Table 3. Individual performance of flowcharts for diagnosing NG and/or CT infection, as reported in individual studies

| Study | Flowchart description | Prevalence (%) | | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|
| | | NG | CT | | |
| **Flowchart 1** – History and risk assessment | | | | | |
| Liu 2003 | WHO algorithm 1 | 69.2 | | 94.6 (227/240) | 41.1 (44/107) |
| Liu 2003 | WHO algorithm 1 | 61.1 | - | 97.2 (206/212) | 37.8 (51/135) |
| Liu 2003 | WHO algorithm 1 | | 23.6 | 91.5 (75/82) | 18.9 (50/265) |
| **Flowchart 2** – History, risk assessment and genital examination | | | | | |
| Bhavsar 2014 | NACO 2 | 88.2 | - | 93.3 (14/15) | 100 (2/2) |
| Chandeying 2000 | WHO algorithm 2 | 50.4 | | 96.9 (63/65) | 7.8 (5/64) |
| Tsai 2008 | WHO algorithm 2 | 47.8 | | 85.0 (136/160) | 40.0 (70/175) |
| Yu 2005 | Taiwan, China locally developed flowchart | 10.1 | - | 58.1 (18/31) | 96.7 268/276 |
| Yu 2005 | Taiwan, China locally developed flowchart | | 14.3 | 31.8 (14/44) | 95.8 (252/263) |
| **Flowchart 3** – History, risk assessment, genital examination and urethral discharge samples for gram staining and microscopy | | | | | |
| Chandeying 2000 | WHO algorithm 2 + microscopy | 32.6 | - | 62.0 (26/42) | not reported |
| Wang 2003 | WHO algorithm + gram stain smear | 64.3 | - | 96.8 202/209 | not reported |
| Wang 2003 | WHO algorithm + gram stain smear | - | 16.3 | 100 (53/53) | not reported |
| Wang 2003 | WHO algorithm + gram stain smear | 72.6 | | 97 (229/236) | 4.5 (4/89) |

CT: *Chlamydia trachomatis;* NACO: National AIDS Control Organization; NG: *Neisseria gonorrhoea;* WHO: World Health Organization

## Pooled results across studies

The pooled diagnostic accuracy of syndromic management for NG and/or CT infections are reported in Table 4; for NG only in Table 5. The certainty of the evidence was LOW due to few events across the studies.

### Table 4. Pooled diagnostic accuracy of urethral discharge flowcharts for NG and/or CT

| Flowchart | N studies | Sensitivity % [95% CI] | Specificity % [95% CI] | Certainty of evidence |
|---|---|---|---|---|
| 1 | 1 | 94.6 [91 - 97] | 41.1 [32 - 51] | LOW |
| 2 | 4 | 85.2 [80.5 – 89] | 66.5 [62.4 - 70.5] | LOW |
| 3 | 2 | 91.7 [87.9 - 94.4] | 4.5* | LOW |

Specificity was reported/calculable in only 1 of the 2 pooled studies.
Flowchart 1 = history and risk assessment; Flowchart 2 = history, risk assessment and genital examination; Flowchart 3 = history, risk assessment, genital examination, and urethral discharge samples for Gram staining and microscopy

### Table 5. Pooled diagnostic validity of urethral discharge flowcharts to diagnose NG only

| Flowchart | N studies | Sensitivity % [95% CI] | Specificity % [95% CI] | Certainty of evidence |
|---|---|---|---|---|
| 1 | 1 | 97.2 [94 - 99] | 37.8 [30 – 47] | LOW |
| 2 | 2 | 69.6 [55.2 - 80.9] | 96 [93.1 - 97.8] | LOW |
| 3 | 2 | 90.8 [86.6 - 93.8] | not estimable* | LOW |

*Specificity was not reported/calculable in any pooled studies.
Flowchart 1 = history and risk assessment; Flowchart 2 = history, risk assessment and genital examination; Flowchart 3 = history, risk assessment, genital examination, and urethral discharge samples for Gram staining and microscopy

## Modelling of effects and costs of syndromic management

Table 6 presents the results of modelling of missed treatment and over treatment for NG and CT, while Table 7 presents hypothetical costs incurred during treatment.

Since the sensitivity and specificity did not follow a pattern as the number of steps in the flowcharts increased (e.g. increasing specificity), it is difficult to make conclusions about the numbers of men who missed treatment (false negatives) with syndromic management. With flowcharts 1, 2 or 3, 30 to 90 men per 1000 missed treatment. When using the hypothetical sensitivity (60 to 80%) and specificity (80 to 90%) of the different point of care tests, the number of men who missed treatment in high prevalence settings (60% with NG/CT) ranged from 120 to 240 per 1000, but with Genexpert, it was 30. In low prevalence settings (10%), it ranged from 20 to 40 per 1000, and was 5 with Genexpert.

There was a large variation in the specificity of the flowcharts, from 4.5% (flowchart 3) to 66.5% (flowchart 2). When modelling using sensitivity (60 to 80%) and specificity (80 to 90%) of the different point of care tests, the number of men who were falsely treated ranged from 40 to 80 per 1000, and 8 with Genexpert in high prevalence settings (60% with NG/CT). In low prevalence settings (10% with NG/CT), it ranged from 90 to 180 per 1000, and 18 with Genexpert.

When adding costs to the model, the overall costs of the flowcharts are lower than the use of a point of care test regardless of the prevalence of NG and CT, but small differences in the costs between the point of care tests. Of note, repeat testing and treatment was not factored into the model for the flowcharts, nor was the future cost of antibiotic resistance in women suspected to have NG or CT.

The results focusing on NG only were also modelled. Table 8 shows the results for flowcharts 1 and 2 (as there were no data for flowcharts 3 and 4 for NG only), point of care tests, and Genexpert. More men missed treatment with flowchart 2, although the difference was less than 100/1000 men even in populations with high prevalence of NG. Similar numbers of men miss treatment with point of care tests at any sensitivity and specificity and with Genexpert. There were also small differences across different prevalence of NG (no more than 100). The number of men who are falsely treated was typically less than 200 for the point of care tests and flowchart 2, but is approximately 500 with flowchart 1. With Genexpert it was less than 20 per 1000 men.

The costs of using flowcharts, point of care tests and Genexpert was also modelled in men to identify NG only (see Table 8). The costs of using flowcharts are lower (~$1500) than the use of a point of care test (~$4000) regardless of the prevalence of NG and CT. The greatest cost is with the use of Genexpert at approximately $17000.

We assumed that antibiotic resistance would develop over time given the treatment of men falsely identified as having gonorrhoea, and therefore modelled the cost of treating gonorrhoea at $25.00 USD, instead of $1.66 USD, and included the costs of the tests and flowcharts (see Table 10). The total cost of using flowchart 2 is the cheapest (ranging from $2500 to $6500 in low to high prevalence settings). The cost of Genexpert is the highest at approximately $20000, then flowchart 1 at approximately $17000, and the lowest cost is flowchart 2 (~$4500). The costs of the point of care tests ranged from $6000 to $13000 across different prevalence of NG.

## Table 6. Modelling of missed treatment and overtreatment for different syndromic management flowcharts and point of care tests for NG and CT in 1000 men with urethral discharge

| | | Prevalence of NG/CT | 100 | 400 | 600 |
|---|---|---|---|---|---|
| sensitivity | specificity | | | | |
| 0.95 | 0.41 | **Flowchart 1** | | | |
| | | TP | 95 | 380 | 570 |
| | | FN - missed treatment | 5 | 20 | 30 |
| | | TN | 369 | 246 | 164 |
| | | FP - false treatment | 531 | 354 | 236 |
| 0.85 | 0.67 | **Flowchart 2** | | | |
| | | TP | 85 | 340 | 510 |
| | | FN - missed treatment | 15 | 60 | 90 |
| | | TN | 603 | 402 | 268 |
| | | FP - false treatment | 297 | 198 | 132 |
| 0.92 | 0.05 | **Flowchart 3** | | | |
| | | TP | 92 | 368 | 552 |
| | | FN - missed treatment | 8 | 32 | 48 |
| | | TN | 45 | 30 | 20 |
| | | FP - false treatment | 855 | 570 | 380 |
| 0.6 | 0.9 | **Point of care 1** | | | |
| | | TP | 60 | 240 | 360 |
| | | FN - missed treatment | 40 | 160 | 240 |
| | | TN | 810 | 540 | 360 |
| | | FP - false treatment | 90 | 60 | 40 |
| 0.7 | 0.8 | **Point of care 2** | | | |
| | | TP | 70 | 280 | 420 |
| | | FN - missed treatment | 30 | 120 | 180 |
| | | TN | 720 | 480 | 320 |
| | | FP - false treatment | 180 | 120 | 80 |
| 0.7 | 0.9 | **Point of care 3** | | | |
| | | TP | 70 | 280 | 420 |
| | | FN - missed treatment | 30 | 120 | 180 |
| | | TN | 810 | 540 | 360 |
| | | FP - false treatment | 90 | 60 | 40 |
| 0.8 | 0.8 | **Point of care 4** | | | |
| | | TP | 80 | 320 | 480 |
| | | FN - missed treatment | 20 | 80 | 120 |
| | | TN | 720 | 480 | 320 |
| | | FP - false treatment | 180 | 120 | 80 |
| 0.8 | 0.9 | **Point of care 5** | | | |
| | | TP | 80 | 320 | 480 |
| | | FN - missed treatment | 20 | 80 | 120 |
| | | TN | 810 | 540 | 360 |
| | | FP - false treatment | 90 | 60 | 40 |
| 0.95 | 0.98 | **Genexpert** | | | |
| | | TP | 95 | 380 | 570 |
| | | FN - missed treatment | 5 | 20 | 30 |
| | | TN | 882 | 588 | 392 |
| | | FP - false treatment | 18 | 12 | 8 |

# Table 7. Modelling of costs for NG and CT in 1000 men with urethral discharge

| Prevalence of NG/CT | 100 | 400 | 600 |
|---|---|---|---|
| **Flowchart 1** (sensitivity 0.95, specificity 0.41) | | | |
| Total test costs | $ - | $ - | $ - |
| Total treatment costs | $ 1,039 | $ 1,218 | $ 1,338 |
| Not cured | 10 | 39 | 59 |
| Adverse events | 93 | 101 | 106 |
| Over treated | 531 | 354 | 236 |
| **Flowchart 2** (sensitivity 0.85, specificity 0.67) | | | |
| Total test costs | $ - | $ - | $ - |
| Total treatment costs | $ 634 | $ 893 | $ 1,066 |
| Not cured | 19 | 77 | 116 |
| Adverse events | 56 | 72 | 83 |
| Over treated | 297 | 198 | 132 |
| **Flowchart 3** (sensitivity 0.92, specificity 0.05) | | | |
| Total test costs | $ 1,000 | $ 1,000 | $ 1,000 |
| Total treatment costs | $ 1,572 | $ 1,557 | $ 1,547 |
| Not cured | 13 | 50 | 76 |
| Adverse events | 142 | 132 | 126 |
| Over treated | 855 | 570 | 380 |
| **Point of care 1** (sensitivity 0.70, specificity 0.80) | | | |
| Total test costs | $ 3,000 | $ 3,000 | $ 3,000 |
| Total treatment costs | $ 249 | $ 498 | $ 664 |
| Not cured | 43 | 172 | 258 |
| Adverse events | 21 | 39 | 50 |
| Over treated | 90 | 60 | 40 |
| **Point of care 2** (sensitivity 0.95, specificity 0.41) | | | |
| Total test costs | $ 3,000 | $ 3,000 | $ 3,000 |
| Total treatment costs | $ 415 | $ 664 | $ 830 |
| Not cured | 34 | 134 | 201 |
| Adverse events | 36 | 53 | 64 |
| Over treated | 180 | 120 | 80 |

| Prevalence of NG/CT | 100 | 400 | 600 |
|---|---|---|---|
| **Point of care 3** (sensitivity 0.95, specificity 0.41) | | | |
| Total test costs | $ 3,000 | $ 3,000 | $ 3,000 |
| Total treatment costs | $ 266 | $ 564 | $ 764 |
| Not cured | 34 | 134 | 201 |
| Adverse events | 22 | 43 | 57 |
| Over treated | 90 | 60 | 40 |
| **Point of care 4** (sensitivity 0.95, specificity 0.41) | | | |
| Total test costs | $ 3,000 | $ 3,000 | $ 3,000 |
| Total treatment costs | $ 432 | $ 730 | $ 930 |
| Not cured | 24 | 96 | 144 |
| Adverse events | 37 | 57 | 71 |
| Over treated | 180 | 120 | 80 |
| **Point of care 5** (sensitivity 0.95, specificity 0.41) | | | |
| Total test costs | $ 3,000 | $ 3,000 | $ 3,000 |
| Total treatment costs | $ 282 | $ 631 | $ 863 |
| Not cured | 24 | 96 | 144 |
| Adverse events | 24 | 48 | 65 |
| Over treated | 90 | 60 | 40 |
| **Genexpert** (sensitivity 0.95, specificity 0.41) | | | |
| Total test costs | $ 16,000 | $ 16,000 | $ 16,000 |
| Total treatment costs | $ 188 | $ 651 | $ 959 |
| Not cured | 10 | 39 | 59 |
| Adverse events | 14 | 48 | 71 |
| Over treated | 18 | 12 | 8 |

Assumptions: Therapy for NG/CT was 1000 mg azithromycin + ceftriaxone 250 mg IM = $1.66; Costs of Flowchart 1, 2 = $0; Flowchart 3 = $1; Costs of Point of Care test = $3; Genexpert costs: $16; Number of people with CT/NG = 75%/25% of true cases; With treatment: 94% CT cure; 98% NG cure; 15% CT adverse events; 3% NG adverse events; Overtreated (FP) 15% adverse events.

# Table 8. Modelling of missed treatment and false treatment for identifying only NG in 1000 men with urethral discharge

| | | Prevalence of NG only | 50 | 200 | 300 |
|---|---|---|---|---|---|
| sensitivity | specificity | | | | |
| 0.97 | 0.38 | **Flowchart 1** | | | |
| | | TP | 49 | 194 | 291 |
| | | FN - missed treatment | 2 | 6 | 9 |
| | | TN | 361 | 304 | 266 |
| | | FP - false treatment | 589 | 496 | 434 |
| 0.70 | 0.96 | **Flowchart 2** | | | |
| | | TP | 35 | 140 | 210 |
| | | FN - missed treatment | 15 | 60 | 90 |
| | | TN | 912 | 768 | 672 |
| | | FP - false treatment | 38 | 32 | 28 |
| 0.6 | 0.9 | **Point of care 1** | | | |
| | | TP | 30 | 120 | 180 |
| | | FN - missed treatment | 20 | 80 | 120 |
| | | TN | 855 | 720 | 630 |
| | | FP - false treatment | 95 | 80 | 70 |
| 0.7 | 0.8 | **Point of care 2** | | | |
| | | TP | 35 | 140 | 210 |
| | | FN - missed treatment | 15 | 60 | 90 |
| | | TN | 760 | 640 | 560 |
| | | FP - false treatment | 190 | 160 | 140 |
| 0.7 | 0.9 | **Point of care 3** | | | |
| | | TP | 35 | 140 | 210 |
| | | FN - missed treatment | 15 | 60 | 90 |
| | | TN | 855 | 720 | 630 |
| | | FP - false treatment | 95 | 80 | 70 |
| 0.8 | 0.8 | **Point of care 4** | | | |
| | | TP | 40 | 160 | 240 |
| | | FN - missed treatment | 10 | 40 | 60 |
| | | TN | 760 | 640 | 560 |
| | | FP - false treatment | 190 | 160 | 140 |
| 0.8 | 0.9 | **Point of care 5** | | | |
| | | TP | 40 | 160 | 240 |
| | | FN - missed treatment | 10 | 40 | 60 |
| | | TN | 855 | 720 | 630 |
| | | FP - false treatment | 95 | 80 | 70 |
| 0.95 | 0.98 | **Genexpert** | | | |
| | | TP | 48 | 190 | 285 |
| | | FN - missed treatment | 3 | 10 | 15 |
| | | TN | 931 | 784 | 686 |
| | | FP - false treatment | 19 | 16 | 14 |

# Table 9. Modelling of costs for testing NG only in 1000 men with urethral discharge

| Prevalence of NG | 50 | 200 | 300 |
|---|---|---|---|
| **Flowchart 1** (sensitivity 0.97, specificity 0.38) | | | |
| Total test costs | $ - | $ - | $ - |
| Total treatment costs | $ 1,403 | $ 1,440 | $ 1,465 |
| Not cured | 2 | 10 | 15 |
| Adverse events | 55 | 47 | 41 |
| Falsely treated for NG | 589 | 496 | 434 |
| **Flowchart 2** (sensitivity 0.70, specificity 0.96) | | | |
| Total test costs | $ - | $ - | $ - |
| Total treatment costs | $ 1,002 | $ 1,072 | $ 1,119 |
| Not cured | 16 | 63 | 94 |
| Adverse events | 140 | 118 | 103 |
| Falsely treated for NG | 38 | 32 | 28 |
| **Point of care 1** (sensitivity 0.6, specificity 0.9) | | | |
| Total test costs | $ 3,000 | $ 3,000 | $ 3,000 |
| Total treatment costs | $ 1,039 | $ 1,092 | $ 1,128 |
| Not cured | 21 | 82 | 124 |
| Adverse events | 131 | 110 | 96 |
| Falsely treated for NG | 95 | 80 | 70 |
| **Point of care 2** (sensitivity 0.7, specificity 0.8) | | | |
| Total test costs | $ 3,000 | $ 3,000 | $ 3,000 |
| Total treatment costs | $ 1,110 | $ 1,163 | $ 1,199 |
| Not cured | 16 | 63 | 94 |
| Adverse events | 116 | 98 | 86 |
| Falsely treated for NG | 190 | 160 | 140 |
| **Point of care 3** (sensitivity 0.7, specificity 0.9) | | | |
| Total test costs | $ 3,000 | $ 3,000 | $ 3,000 |
| Total treatment costs | $ 1,042 | $ 1,106 | $ 1,149 |
| Not cured | 16 | 63 | 94 |
| Adverse events | 131 | 110 | 96 |
| Falsely treated for NG | 95 | 80 | 70 |
| **Point of care 4** (sensitivity 0.8, specificity 0.8) | | | |
| Total test costs | $ 3,000 | $ 3,000 | $ 3,000 |
| Total treatment costs | $ 1,113 | $ 1,177 | $ 1,220 |
| Not cured | 11 | 43 | 65 |
| Adverse events | 116 | 98 | 86 |
| Falsely treated for NG | 190 | 160 | 140 |
| **Point of care 5** (sensitivity 0.8, specificity 0.9) | | | |
| Total test costs | $ 3,000 | $ 3,000 | $ 3,000 |
| Total treatment costs | $ 1,046 | $ 1,120 | $ 1,170 |
| Not cured | 11 | 43 | 65 |
| Adverse events | 131 | 110 | 96 |
| Falsely treated for NG | 95 | 80 | 70 |
| **Genexpert** (sensitivity 0.95, specificity 0.98) | | | |
| Total test costs | $ 16,000 | $ 16,000 | $ 16,000 |
| Total treatment costs | $ 997 | $ 1,096 | $ 1,162 |
| Not cured | 3 | 14 | 21 |
| Adverse events | 142 | 120 | 105 |
| Falsely treated for NG | 19 | 16 | 14 |

Assumptions: Therapy for all positives (NG) was 1000 mg azithromycin + ceftriaxone 250 mg IM = $1.66; Therapy for negatives was 1000 mg azithromycin = $0.95. Costs of Flowchart 1, 2 = $0; Costs of Point of Care test = $3; Genexpert costs: $16; With treatment: 98% NG cure; 15% dual therapy adverse events; Overtreated (FP) 15% dual therapy adverse events; negatives treated with azithromycin – adverse events 15%.

# Table 10. Modelling of costs of antimicrobial resistance for NG in 1000 men with urethral discharge

| Prevalence of NG | 50 | 200 | 300 |
|---|---|---|---|
| **Flowchart 1** (sensitivity 0.97, specificity 0.38) | | | |
| Total test costs | $ - | $ - | $ - |
| Total treatment costs | $ 16,282 | $ 17,545 | $ 18,386 |
| Not cured | 2 | 10 | 15 |
| Adverse events | 55 | 47 | 41 |
| Falsely treated for NG | 589 | 496 | 434 |
| **Flowchart 2** (sensitivity 0.70, specificity 0.96) | | | |
| Total test costs | $ - | $ - | $ - |
| Total treatment costs | $ 2,706 | $ 5,087 | $ 6,674 |
| Not cured | 16 | 63 | 94 |
| Adverse events | 140 | 118 | 103 |
| Falsely treated for NG | 38 | 32 | 28 |
| **Point of care 1** (sensitivity 0.6, specificity 0.9) | | | |
| Total test costs | $ 3,000 | $ 3,000 | $ 3,000 |
| Total treatment costs | $ 3,956 | $ 5,760 | $ 6,963 |
| Not cured | 21 | 82 | 124 |
| Adverse events | 131 | 110 | 96 |
| Falsely treated for NG | 95 | 80 | 70 |
| **Point of care 2** (sensitivity 0.7, specificity 0.8) | | | |
| Total test costs | $ 3,000 | $ 3,000 | $ 3,000 |
| Total treatment costs | $ 6,361 | $ 8,165 | $ 9,368 |
| Not cured | 16 | 63 | 94 |
| Adverse events | 116 | 98 | 86 |
| Falsely treated for NG | 190 | 160 | 140 |
| **Point of care 3** (sensitivity 0.7, specificity 0.9) | | | |
| Total test costs | $ 3,000 | $ 3,000 | $ 3,000 |
| Total treatment costs | $ 4,077 | $ 6,241 | $ 7,684 |
| Not cured | 16 | 63 | 94 |
| Adverse events | 131 | 110 | 96 |
| Falsely treated for NG | 95 | 80 | 70 |
| **Point of care 4** (sensitivity 0.8, specificity 0.8) | | | |
| Total test costs | $ 3,000 | $ 3,000 | $ 3,000 |
| Total treatment costs | $ 6,482 | $ 8,646 | $ 10,089 |
| Not cured | 11 | 43 | 65 |
| Adverse events | 116 | 98 | 86 |
| Falsely treated for NG | 190 | 160 | 140 |
| **Point of care 5** (sensitivity 0.8, specificity 0.9) | | | |
| Total test costs | $ 3,000 | $ 3,000 | $ 3,000 |
| Total treatment costs | $ 4,197 | $ 6,722 | $ 8,406 |
| Not cured | 11 | 43 | 65 |
| Adverse events | 131 | 110 | 96 |
| Falsely treated for NG | 95 | 80 | 70 |
| **Genexpert** (sensitivity 0.95, specificity 0.98) | | | |
| Total test costs | $ 16,000 | $ 16,000 | $ 16,000 |
| Total treatment costs | $ 2,549 | $ 5,904 | $ 8,141 |
| Not cured | 3 | 14 | 21 |
| Adverse events | 142 | 120 | 105 |
| Falsely treated for NG | 19 | 16 | 14 |

Assumptions: Combination therapy for NG/CT = $25; Costs of Flowchart 1, 2 = $0; Costs of Point of Care test = $3; Genexpert costs: $16; With treatment for NG/CT (TP, FP): 98% NG cure assumed; 15% adverse events; with treatment for CT (FN, TN): 15% adverse events; Long term consequences of missed treatment for NG (e.g., repeat tests) not calculated

# 4. FUTURE RESEARCH

We looked for but did not find studies that followed men with urethral discharge who were or were not treated using syndromic management. We found very few studies that evaluated the sensitivity or specificity of different syndromic strategies (or flowcharts). In fact, there were 6 studies, most with small numbers of men, and many did not report the specificity of the flowchart or data to calculate a specificity. It was also often unclear which flowchart was being used in the studies, and although two investigators assessed the flowcharts, and finally did agree on how to classify the study, it is possible that the flowcharts were incorrectly categorised.

We calculated the number of men who were treated or not treated, and the costs based on the pooled estimates of sensitivity and specificity across studies. Unfortunately, most pooled estimates were based on 1 to 2 studies, with few men which resulted in imprecise numbers, and therefore low certainty in the pooled estimates. Studies assessing the diagnostic accuracy or different flowcharts are needed, simply to increase the numbers of participants and increase our certainty in the results.

The models we performed are based on what happens to men who present with urethral discharge if managed syndromically or if tested for NG using point of care tests with various sensitivities and specificities. It should be stressed that the modelling was based on men who have urethral discharge, and the risk of antimicrobial resistance was again modelled on this population of men. Other modelling could be conducted to determine the use of these tests in men who may present to a clinic or health care provider for any reason not necessarily for urethral discharge. Testing could possibly be provided to men based on specific risk factors for NG/CT. We have only considered the risk factor of urethral discharge, but other characteristics could be used, such as having sex with men, having multiple partners, and working in a position that requires travel. In those populations, point of care tests could prove to be cost saving, reduce over treatment, and increase appropriate treatment.

While additional research and modelling should be conducted, the information presented in this report can be used to inform decisions about providing syndromic management of urethral discharge and about the need for point of care tests for NG.

# 5. REFERENCES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3. WHO. Sexually transmitted and other reproductive tract infections: A guideline to essential practice. Geneva2005.
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# OTHER ETD FACTORS ASSOCIATED WITH SYNDROMIC MANAGEMENT OF URETHRAL DISCHARGE

## 6. METHODS

### Search Strategy

Database: Embase <1996 to 2020 February 25>

Search Strategy:

1. (urethr* or penis or penile).mp. (97247)
2. (discharge* or secrete* or secretion*).mp. (864881)
3. milk*.mp. (125303)
4. 1 and (2 or 3) (4891)
5. exp algorithm/ (277738)
6. flowcharts.mp. (395)
7. Flowchart.mp. (1534)
8. algorithm.mp. (362206)
9. algorithms.mp. (109816)
10. flow charts.mp. (465)
11. flow chart.mp. (1598)
12. clinical pathway.mp. (9853)
13. clinical pathways.mp. (2999)
14. risk assessment.mp. (547256)
15. syndromically.mp. (65)
16. syndromic.mp. (15121)
17. signs.ti,ab. (326403)
18. symptoms.mp. (1105979)
19. symptom.mp. (479924)
20. sign.ti,ab. (95797)
21. decision tree.mp. (15139)
22. decision trees.mp. (2422)
23. syndromic approach.mp. (300)
24. syndromic diagnosis.mp. (405)
25. syndromic management.mp. (429)
26. syndromic approaches.mp. (13)
27. (algorithm or flowcharts or Flowchart or algorithm or algorithms or flow charts or flow chart or clinical pathway or clinical pathways or risk assessment or syndromically or syndromic or signs or symptoms or symptom or sign or decision tree or decision trees or syndromic approach or syndromic diagnosis or syndromic management or syndromic approaches).mp. (2535755)
28. 4 and 27 (1558)
29. feasib*.tw. (413408)
30. sustain*.tw. (391234)
31. access*.tw. (586042)
32. viab*.tw. (323365)
33. constrain*.tw. (135642)
34. barrier*.tw. (320413)
35. facilitat*.tw. (565382)
36. coverage*.mp. (141139)
37. legal*.mp. (189510)
38. financ*.mp. (196670)
39. cost*.mp. (918854)

40. resource*.mp. (414423)
41. exp Health Knowledge, Attitudes, Practice/ (96703)
42. Interprofessional Relations/ or public relations/ (38514)
43. implement*.mp. (589523)
44. (program* and evaluat*).mp. (329199)
45. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 (4391787)
46. (exp Gender Identity/ or exp Gender/) and Sex/ (416)
47. (gender-based or gender related or gender factors).tw. (9973)
48. ((sex or gender) adj3 (analysis or factor$ or inequit$ or disparit$ or inequalit$ or difference$ or interact$)).tw. (149707)
49. exp Sex Factors/ (6779)
50. exp Geriatrics/ (26902)
51. ((ethnic$ or race or racial or religio$ or cultur$ or minorit$ or refugee or indigenous or aboriginal or African american) adj3 (analysis or disparit$ or inequalit$ or inequit$ or difference$ or predict$ or interact$)).tw. (74921)
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53. exp Disabled Persons/ (38167)
54. ((poverty or low-income or "lower income" or socioeconomic$ or socio-economic$ or social) adj3 (analysis or disadvantage$ or factor$ or inequalit$ or depriv$ or inequit$ or disparit$ or difference$ or predict$ or interact$)).tw. (100579)
55. exp Educational Status/ (68667)
56. exp Socioeconomic Factors/ (301696)
57. ((discriminat$ or social exclu$ or social inclu$) adj3 (religion or culture or race or racial or aboriginal or indigenous or ethnic$)).tw. (2005)
58. ((urban or rural or inner-city or remote or slum) adj3 (analysis or inequit$ or disparit$ or inequalit$ or difference$ or predict$ or interact$)).tw. (7685)
59. ((resource-poor or ("low income" adj countr$) or ("middle income" adj countr$) or africa or developing countr$ or "south america" or china or asia or "latin america") adj3 (relevance or analysis or applicab$ or inequit$ or disparit$ or inequalit$ or difference$ or predict$ or interact$)).tw. (6186)
60. (inequalit$ or in-equalit$ or equit$ or inequit$ or in-equit$ or disparit$ or underserved or marginali$ed).tw. (136652)
61. exp Population Groups/ (915778)
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63. (first adj2 nation*).tw. (6640)
64. (aborigin$ or metis or inuit$ or eskimo$ or native or esquimaux or aleut or yuit or inughuit or unanga* or alutiiq or inup#ia* or kalaallit or Inuktitut or Nunavut or nunavik or cree or dene or haida or salish or Mohawk or ojibway or yupik or tribal or arctic).tw. (221000)
65. exp american native continental ancestry group/ or oceanic ancestry group/ (16364)
66. exp Rural Health/ (940)
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69. exp Patient Preference/ (17668)
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71. xp Physician-Patient Relations/ (2434)
72. exp Health Knowledge, Attitudes, Practice/ (96703)
73. "Attitude of Health Personnel"/ (52845)

74. exp Practice Patterns, Physicians'/ or clinical practice/ (272166)
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76. prefer*.mp. (484033)
77. attitude*.mp. (426906)
78. feeling*.mp. (75387)
79. thought*.mp. (296668)
80. perception*.mp. (361683)
81. perspective*.mp. (339249)
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83. knowledge*.mp. (801886)
84. view*.mp. (459625)
85. deci*.mp. (788634)
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92. 89 or 90 or 91 (810)
93. limit 92 to yr="2010 -Current" (619)
94. remove duplicates from 93 (614)

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1. exp "Patient Acceptance of Health Care"/ (147845)
2. exp Patient Preference/ (8027)
3. exp Patient Satisfaction/ (87633)
4. exp Physician-Patient Relations/ (71615)
5. exp Health Knowledge, Attitudes, Practice/ (108377)
6. "Attitude of Health Personnel"/ (119601)
7. exp Practice Patterns, Physicians'/ or clinical practice/ (58158)
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23. sustain*.tw. (335146)
24. access*.tw. (492341)
25. viab*.tw. (282128)
26. constrain*.tw. (134964)
27. barrier*.tw. (281923)
28. facilitat*.tw. (511986)
29. coverage*.mp. (124888)
30. legal*.mp. (121533)
31. financ*.mp. (153826)
32. cost*.mp. (684485)
33. resource*.mp. (372609)

34. exp Health Knowledge, Attitudes, Practice/ (108377)
35. Interprofessional Relations/ or public relations/ (57535)
36. implement*.mp. (472478)
37. (program* and evaluat*).mp. (261983)
38. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 (3729141)
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40. (gender-based or gender related or gender factors).tw. (7947)
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42. exp Sex Factors/ (259563)
43. exp Geriatrics/ (29680)
44. ((ethnic$ or race or racial or religio$ or cultur$ or minorit$ or refugee or indigenous or aboriginal or African american) adj3 (analysis or disparit$ or inequalit$ or inequit$ or difference$ or predict$ or interact$)).tw. (62532)
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46. exp Disabled Persons/ (64114)
47. ((poverty or low-income or "lower income" or socioeconomic$ or socio-economic$ or social) adj3 (analysis or disadvantage$ or factor$ or inequalit$ or depriv$ or inequit$ or disparit$ or difference$ or predict$ or interact$)).tw. (91633)
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49. exp Socioeconomic Factors/ (441245)
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51. ((urban or rural or inner-city or remote or slum) adj3 (analysis or inequit$ or disparit$ or inequalit$ or difference$ or predict$ or interact$)).tw. (7316)
52. ((resource-poor or ("low income" adj countr$) or ("middle income" adj countr$) or africa or developing countr$ or "south america" or china or asia or "latin america") adj3 (relevance or analysis or applicab$ or inequit$ or disparit$ or inequalit$ or difference$ or predict$ or interact$)).tw. (5273)
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54. exp Population Groups/ (292280)
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56. (first adj2 nation*).tw. (5307)
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58. exp american native continental ancestry group/ or oceanic ancestry group/ (30861)
59. exp Rural Health/ (23244)
60. 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 (1527620)
61. (urethr* or penis or penile).mp. (95256)
62. (discharge* or secrete* or secretion*).mp. (722658)
63. milk*.mp. (143550)
64. 61 and (62 or 63) (2794)
65. Software Design/ (5885)
66. flowcharts.mp. (287)
67. Flowchart.mp. (967)
68. algorithm.mp. (178808)
69. algorithms.mp. (299691)
70. flow charts.mp. (368)
71. flow chart.mp. (1093)

72. clinical pathway.mp. (1951)
73. clinical pathways.mp. (1926)
74. risk assessment.mp. (290309)
75. syndromically.mp. (43)
76. syndromic.mp. (11387)
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78. symptoms.mp. (873297)
79. symptom.mp. (201808)
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81. syndromic approach.mp. (240)
82. syndromic diagnosis.mp. (245)
83. syndromic management.mp. (331)
84. syndromic approaches.mp. (7)
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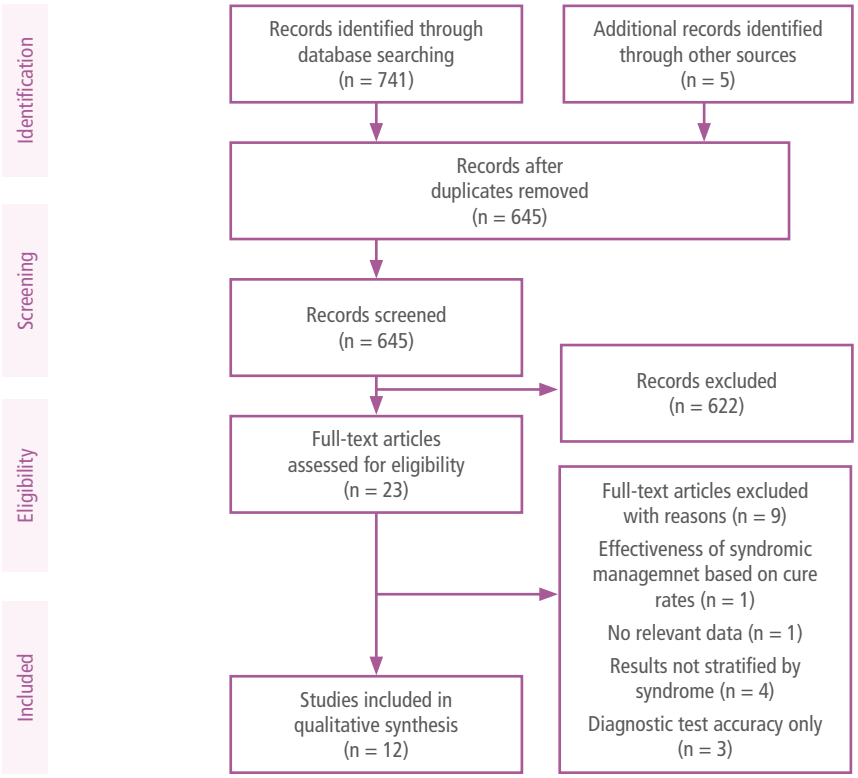
86. 85 and 64 (724)
87. 21 and 86 (183)
88. 38 and 86 (132)
89. 60 and 86 (103)
90. 87 or 88 or 89 (323)
91. limit 90 to yr="2010 -Current" (122)
92. remove duplicates from 91 (122)

## Study selection

We included studies published in 2010 to present that focused on the acceptability, feasibility, equity, and resources/costs associated with syndromic management of urethral discharge. We excluded animal studies, case reports, conference abstracts, commentaries, opinion pieces and editorials, and those studies that did not report results stratified by syndrome (e.g., studies reporting on the causes of delay in seeking treatment for all urethral discharge and vaginal discharge combined). There were no language filters applied.

# 7. RESULTS

## Figure 4. PRISMA 2009 Flow Diagram



# Table 11. Study characteristics of all included studies

| Reference | Country | Description of study | Year | Healthcare sector |
|---|---|---|---|---|
| Khan 2012 | Pakistan | • In-depth interviews & focus groups with 51 providers<br>• demographics of patients, environment of facilities, knowledge & adherence to STI guidelines, case management practices, including medication prescription | 2008 | Public and private, including NGO clinics |
| Hoffman 2019 | South Africa | • adults >18y with STI symptoms (dysuria, discharge) mobilized through posters at public health clinics, community health workers and traditional healers<br>• men and women treated at public health clinics by syndromic surveyed | 2017-2018 | Public |
| Aaron 2019 | United States | • 385 men ≥18y presenting to clinic with complaints of urethritis (urethral discharge and/or dysuria) asked about onset of symptoms, reasons for delay, and concerns prior to seeking treatment | 2017 | Public |
| Alemayehu 2015 | Ethiopia | • healthcare professionals and STI patients in Gama Gofa Zone<br>• questionnaire testing provider knowledge of STI syndromes, retrospective review of patient cards to assess adequacy of management in past, mystery clients (standardized patients) used to assess practice of clinicians | 2015 | Public |
| Iipinge 2012 | Namibia | • 50 healthcare providers surveyed<br>• Determined whether providers follow STI management guidelines via face-to-face interviews or self-administered questionnaire, observation of facility to determine the availability of essential resources | NR | Private |
| Kohler 2017 | South Africa | • 195 visits by standard patients 22-47y sent to 1 or more of 50 randomly selection clinical sentinel surveillance sites, stratified by province<br>• Males reported urethral discharge for 3 days and were uncircumcised<br>• Determined adequacy of STI care | 2014 | Public |
| Korenromp 2017 | NA | • Estimates of costs of implementing WHO's global strategy of STIs | NA | NA |
| Weaver 2016 | South Africa | • 40 stationary public health clinics allocated to 1 of 3 interventions modalities for training in syndromic management (lecture, paper based, computer based)<br>• Male standardized patients presented with urethral discharge whole females presented with vaginal discharge to assess adequacy of syndromic management | 2013 | Public |

| Reference | Country | Description of study | Year | Healthcare sector |
|---|---|---|---|---|
| Garcia 2012 | Peru | • Physicians, midwives and pharmacy workers trained based on randomization of intervention at the city level. Intervention included training of clinicians and pharmacy workers in identifying and managing STI syndromes and preventative counselling via seminars and workshops, ongoing structural support of network of practitioners ("Prevention salesperson"), and continuing education<br>• Adequacy of syndromic management assessed by sending standardized patients to clinics. Management of urethral discharge considered adequate if patient offered treatment for gonorrhea and chlamydia in accordance with national guidelines | | Public |
| Adhikari 2014 | Nepal | • Cross-sectional study of knowledge and practices of 54 male auxiliary health workers who are trained in syndromic case management/reproductive health compared to those untrained | 2005 | Public |
| Ham 2016 | South Africa | • survey of 611 doctors and nurses<br>• self-administered survey – pictures and patient histories presented. Providers asked to identify STI syndrome, possible aetiologies, proper management | 2008-2009 | Public and private |
| Leichliter 2011 | South Africa | • 58 men ≥18y recruited throughout the community for focus groups<br>• Collected information on cultural/group norms, attitudes, beliefs regarding access to sexual health care in men | 2007 | NA |
| Hussain 2011 | Pakistan | • survey administered to 103 general practitioners (with at least MBBS)<br>• questions included: treatment regimens for urethral discharge, how clinician would examine patient, and what information necessary to have complete patient history | 2007-2008 | Private |

# 8. ACCEPTABILITY

## Acceptability of STI care by syndromic management (patient perspective)

Leichliter and colleagues (1) recruited a sample of men from the Johannesburg metropolitan area (Gauteng Province, South Africa) for a focus group to collect information on beliefs norms, attitudes, and beliefs regarding access to sexual health care in men. Public health centers in South Africa use syndromic management; men cited competent nurses, convenience of location, free service and better quality of care as compared to traditional healers as facilitators of seeking sexual health care at public health clinics. A preponderance (77.7%) of standardized patients receiving care in 1 or more of 50 public health care facilities in South Africa as men with urethral discharge syndrome reported that they felt treated with respect and understanding, while only 3.5% felt judged by the provider (2).When discussing alternatives to STI care at a public health facility, some men preferred traditional healers because of perceived expedited care, convenience of location and more privacy. Increased privacy was also a benefit of care at a private health care clinic, second to a perceived higher quality of care; however, high costs at private clinics were seen as a deterrent to seeking care in the private sector (1).

## Acceptability of STI care by syndromic management (clinician perspective)

### Acceptability of clinicians to apply intervention

Heterogeneity in the appropriate implementation of syndromic management has been highlighted in the literature. Khan and Khan (3) report STI care in Pakistan differs greatly depending on whether it is sought in the public or private sectors. Some public sector healthcare providers knew of STI management guidelines but expressed uncertainty as to efficacy of syndromic management. General practitioners sometimes followed syndromic management guidelines, whereas STI care providers in non-governmental organization (NGO) clinics usually followed published guidelines for syndromic management. In an assessment of the quality of STI care provided by general practitioners in private clinics in Windhoek, Namibia, Iipinge and Pretorius (4) report that 57% of patients with urethral discharge were managed correctly according to the syndromic approach. 43% of men were prescribed treatments that were not recommended for patients presenting with urethral discharge for the first time, while 26% and <10% of men were encouraged to notify partners and were provided with condoms at first consultation. Only a third of patients underwent thorough examinations, and 32-35% of men received counselling. Kohler and colleagues (2) assessed the quality of STI in 50 public health facilities in South Africa via standardized patients. During 186 successful clinics by male and female actors, 25.1% of actors presenting with urethral discharge were offered all essential STI services (i.e., treatment consistent with national guidelines, receipt of ≥1 condom, partner notification slip or counselling), 70.7% received appropriate medication while 20.1% received inappropriate medication as per national guidelines. Weaver and colleagues (5) report higher rates of inappropriate medication prescription in their study of STI care in South African public health clinics using standardized patients: 64% of men were prescribed the incorrect treatment, while 32% of men did not receive any drugs to treat STIs.

# 9. FEASIBILITY

## Barriers to seeking treatment (patient perspective)

Hoffman and colleagues (6) mobilized men experiencing symptoms of urethral discharge in Mopani District, South Africa to seek STI-related care at public health clinics via posters displayed in public health clinics, and by training community health workers and traditional leaders about the signs and symptoms associated with STIs. 72% of men recruited had experienced symptoms for over 30 days and delaying treatment. 37% of men did not seek care as a result of their own knowledge and beliefs (e.g., being unaware of symptoms or having traditional beliefs), 33% did not seek care due to factors associated with healthcare itself (e.g., lack of male workers or being disappointed with previous health services), while the remaining third of men opted to forgo treatment because of disappointment with care or because symptoms were persistent or recurrent. Among men presenting to a public STI clinic in the United States after complaints of symptoms of urethral discharge and/or dysuria, those reporting that they delayed seeking treatment were more likely to have attempted home remedies versus those seeking care within 7 days of symptom onset (7).

Other studies report the paucity of male healthcare workers at public health clinics in South Africa. Weaver *et al.* (5), in their study assessing the effectiveness of training for health care professionals, report that 93% of standardized patients encountered female clinicians when sent to 1 or more of 40 different stationary public health clinics. Similarly, Leichliter *et al.* (1) noted respondents in their focus groups remarking "clinics aren't meant for men," owing to the high visibility of women providing and seeking care at public health clinics. In a similar vein, Ham and colleagues (8), in their cross-sectional survey capturing provider's attitudes and beliefs regarding patients with STIs, revealed that male patients are more willing to discuss symptoms and have genital examinations when treated by male practitioners as opposed to being treated by female practitioners.

Leichliter and colleagues' (1) focus groups highlighted a number of additional barriers to seeking STI care at public health clinics, including: long lines, displeasure with healthcare providers, limited information provided by healthcare workers, and lack of confidentiality. Some men attending public health clinics perceived lack of compassion and/or respect for them from clinic staff, and felt that they were being criticized by staff in front of other patients. Some men recounted lack of physical examination at public health clinics before being prescribed medications and cited this as a deterrent to seeking STI care at public centers. Expediency of consultation and treatment, convenience of location, affordable costs and privacy were highlighted as important factors in deciding whether to seek STI care at a public or private health care facility, or whether to seek treatment with a traditional healer (1).

## Barriers to providing treatment (clinician's perspective)

### Provisions related to STI care

Providers felt that additional time, educational pamphlets, visual aids, and a more consistent supply of STI medications would help them provide patients with better care (8).

### Knowledge of syndromic management of STIs

Numerous studies report on healthcare providers' knowledge of correctly managing urethral discharge syndrome. Ham *et al.* (8) report that 92% of healthcare providers in Gauteng Province, South Africa identified urethral discharge syndrome correctly when presented with pictures and patient history, while only 40% identified treatment regimens accurately. Alemayehu and colleagues (9) reported 47.6% of health professionals surveyed in Gamo Gofa Zone, Ethiopia were able to correctly identify the name of drugs recommended by national guidelines for the treatment of urethral discharge, while 27.2% were able to name dosages, frequency and duration of treatment in addition to identifying drugs. 55.3% of general practitioners in private facilities across Karachi, Pakistan, knew the WHO recommended treatment regimen for urethral discharge (10), while 63% and 51.9% of male auxiliary health workers in Nepal were knew how to accurately diagnose and treat urethral discharge, respectively (11).

The impact of training on provider knowledge of urethral discharge on diagnosis and adequate management has also been reported. Though Alemayehu and colleagues (9) report no significant impact of training on knowledge of urethral discharge, auxiliary health workers in Nepal who reported having training in syndromic management were more likely to correctly diagnose and know which medication to prescribe to men presenting with urethral discharge (11) , as did healthcare providers in Gauteng Province, South Africa (8). General knowledge of urethral discharge was increased by 7.9% among practitioners at public health clinics allocated to lecture, computer or paper-based interventions in South Africa (5). In Peru, adequate management of urethral discharge (i.e., standardized patients offered treatment of gonorrhea and chlamydia that followed national guidelines) increased 50-70% at 3, 6 and 18 months in cities where physicians, midwives and pharmacy workers were randomized to intervention including seminars, workshops, structural support networks, and continuing education compared to those cities with no intervention (12).

# 10. EQUITY

## Inequities in access to appropriate syndromic management of STIs

Studies have reported differences in overall knowledge and practice of healthcare practitioners based on level of clinical training and healthcare setting. Among Ethiopian health professionals in public health care settings, medical doctors and health officers had significantly more knowledge of urethral discharge as compared to diploma nurses, while clinicians working in health centers were significantly more knowledgeable than those practicing in hospitals (9) . In Gauteng Province, South Africa, nurses as opposed to physicians were more likely to correctly identify of the recommended treatments for urethral discharge, as were practitioners in the public setting compared to the private setting (8). In Pakistan, only non-governmental organization (NGO) STI clinics have adopted syndromic management STIs. Quality of care received at NGO clinics, however, still appears suboptimal (3). In Namibia, medical aid does not seem to affect the management of patients with urethral discharge attending private health care clinics (4).

# 11. RESOURCES AND COSTS

Korenromp *et al.* (13) estimate the average cost of treatment for gonorrhea, chlamydia and mycoplasma, and trichomoniasis to be USD $10.71, 10.95, and 10.05, respectively, including the cost of drugs and service delivery based on syndromic management. Point-of-care tests for gonorrhea and chlamydia (NAAT, nucleic acid amplification test), and trichomoniasis (wet mount) are estimated to cost USD $13.00 and USD $4.00, respectively, including cost of drugs and service delivery.

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